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RHÔNE-POULENC

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October 27, 1992

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Office of Toxic Substances
US Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company (RPAC), the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on M&B 46030. Its CAS number and chemical index name are 120068-37-3 and 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile. This chemical is manufactured in Europe and imported by RPAC for pesticide research and development.

No claims of confidentiality are made for this submission. Please note that RPAC released previous confidentiality claims for the subject chemical on September 8, 1992. The title of the enclosed report is "M&B 46030 Toxicity to Rats by Repeated Oral Administration for 2 Weeks". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of the observation of increased liver and thyroid weights and histological changes in these organs. Groups of 5 male and 5 female CD rats were administered test material by gavage at doses of 0, 1, 3, 10, or 30 mg/kg/day for two weeks. Two males and one female died at 30 mg/kg/day. Mean liver weight for males and females given 10 and 30 mg/kg/day and females given 3 mg/kg/day was significantly increased. Mean thyroid weights were increased at all dose levels, but the increases did not follow a dose-response pattern. Histologically, centrilobular hepatocyte enlargement was noted in 10 and 30 mg/kg/day males and centrilobular hepatocyte vacuolation in 30 mg/kg/day males. The thyroids showed minimal or moderate follicular cell hypertrophy in males and females at 3, 10, and 30 mg/kg/day. One female at 1 mg/kg/day also showed this effect.

3/1/95

Seven previous TSCA Section 8(e) notices were submitted on this chemical. The EPA Document Control Numbers for these submissions are 8EHQ-0191-1162S, 8EHQ-0391-1199S, 8EHQ-0591-1232S, 8EHQ-0791-1284S, 8EHQ-0791-1285S and 8EHQ-0891-1315S, and 8EHQ-0392-2540S. Also several Section 8(e) notices will be submitted on this compound under the CAP.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,

Glenn S. Simon, PhD, DABT
Director of Toxicology

CONFIDENTIAL

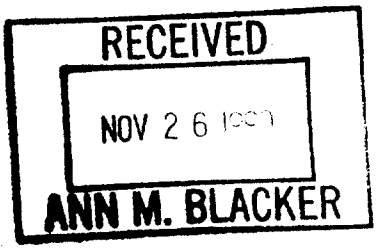
M&B 309/89343

M&B 46,030

TOXICITY TO RATS

BY REPEATED ORAL ADMINISTRATION

FOR 2 WEEKS



Addressee:

Rhône-Poulenc Ltd.,
Rainham Road South,
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RM10 7XZ.

Report issued 25 July 1989

Principal Authors:

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Huntingdon Research Centre Ltd.,
P.O. Box 2,
HUNTINGDON,
Cambridgeshire,
PE18 6ES.

We the undersigned, hereby declare that the work was performed under our supervision according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.

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CONTENTS M&B/309

APPENDICES

ADDENDA

Test material: M&B 46,030.

Test species: Charles River (U.S.A.) CD rats of Sprague-Dawley origin.

Route of administration: Oral gavage.

Dosage levels:

Group	Dosage (mg/kg/day)	Number of animals
1	Control (0)	5♂ and 5♀
2	1	5♂ and 5♀
3	3	5♂ and 5♀
4	10	5♂ and 5♀
5	30	5♂ and 5♀

Dosing commenced: 29 September 1988.

Duration: 2 weeks.

Necropsy: 13/14 October 1988.

Results

Mortality: Two males and one female given 30 mg/kg/day were found dead on Day 4/5 of treatment. Although clinical and macroscopic findings did not indicate the cause of these deaths, they were considered to be due to treatment with M&B 46,030.

In addition, one female control animal died following blood sampling on Day 14. This death was considered to be accidental.

Clinical signs: Muscular spasms were noted on one occasion for each of a few animals given 30 mg/kg/day.

Bodyweight:	Bodyweight losses were noted after 4 days of treatment for most surviving animals given 30 mg/kg/day and one female given 10 mg/kg/day. Mean weight change during this period for males given 10 mg/kg/day and for males and females given 30 mg/kg/day was significantly lower than that of controls. Subsequently, the weight gain of these rats was similar to or marginally superior to that of the controls.
Food consumption:	During the first week of treatment, the food consumption by males and females given 30, 10 or 3 mg/kg/day and females given 1 mg/kg/day was lower than that of controls to a dosage-related degree. There were no notable group differences in food intake during the second week of treatment.
Efficiency of food utilisation:	**An inferior efficiency of food utilisation was noted during Week 1 only for males and females given 30 mg/kg/day, when compared with controls.**
Water consumption:	Treatment with M&B 46,030 was not considered to have affected the water consumption of treated groups.
Ophthalmoscopy:	There were no treatment-related findings.
Haematology:	There were no findings considered to be of toxicological importance.
Biochemistry:	Statistically significant increases in plasma globulin concentration were observed for males given 3 or 10 mg/kg/day and for males and females given 30 mg/kg/day when compared with controls. Associated increases in total plasma protein were observed for these groups although statistical significance was not attained. The remaining findings were not considered to be of toxicological importance.

Urinalysis:	There were no treatment-related findings.
Organ weights:	Mean liver weight for males and females given 10 or 30 mg/kg/day and females given 3 mg/kg/day was significantly greater than that of controls. Mean thyroid weight for all female treated groups was greater than that of control, attaining statistical significance at all dosage levels. However, there was no dosage-dependency. A similar trend was also noted for all male treated groups, also without dosage-dependency, but statistical significance was not attained.
Macroscopic pathology:	**There were no macroscopic findings considered to be attributable to treatment with M&B 46,030.**
Microscopic pathology:	Liver: Minimal centrilobular hepatocyte enlargement was noted in 3/5 males given 10 mg/kg/day and 3/5 males given 30 mg/kg/day. Thyroids: Minimal or moderate follicular cell hypertrophy was noted in males and females given 3, 10 or 30 mg/kg/day in a dosage-related manner. One female given 1 mg/kg/day also showed minimal follicular cell hypertrophy with epithelial vacuolation.

Conclusion

The administration of M&B 46,030 to rats by repeated oral gavage at a dosage of 30 mg/kg/day resulted in the death of 2 males and 1 female after 3 or 4 days of treatment. Other effects principally included isolated reports of muscular spasms at 30 mg/kg/day and, predominantly at this dosage level, a transient adverse effect on weight gain and food intake. Increases in total plasma protein and the globulin fraction were also observed principally at a dosage level of 30 mg/kg/day.

The liver and thyroids were identified as target organs; mean liver weight was increased at dosages of more than 3 mg/kg/day, while mean thyroid weight was increased at all dosage levels. These changes were associated with minimal centrilobular hepatocyte enlargement and minimal or moderate follicular cell hypertrophy respectively.

The object of this study, performed at the Huntingdon Research Centre Ltd., England, was to assess the toxicity of the test material, M&B 46,030 to rats by repeated oral administration over a period of two weeks.

The dosage levels used in this study were chosen by the Sponsor, with reference to available toxicity data. The test species was chosen according to regulatory requirements and the Sprague-Dawley strain of rat was chosen due to the availability of background data at this laboratory. The oral route was chosen as it is the anticipated route of human exposure to the test material.

This report contains all the relevant data generated during the study.

Relevant dates in the study:

Protocol approval:

Study Director:	19 August 1988.
HRC Management:	19 August 1988.
Sponsor:	24 August 1988.
Animal arrival:	15 September 1988.
Start of treatment:	29 September 1988.
Necropsy:	13/14 October 1988.

Test material

The Sponsor was responsible for characterisation of the test material. The following information is given in summary:

Test material:	M&B 46,030.
Supplier:	Sponsor.
Action:	Pesticide.
Description of material:	White solid.
Storage conditions:	Closed container at room temperature in the dark.
Stability of test material:	Not specified.
Stability of formulations:	Not specified.
Date of receipt at HRC:	12 August 1988.
Batch no.:	IGB 464.
Purity:	Not specified.

Animal management

A total of 88 Crl: CD (SD) BR rats (43 males and 45 females) approximately 28 days old and within a weight range of 13 g for males and 10 g for females was obtained from Charles River Laboratories Inc., Portage, Michigan, U.S.A.

On arrival, 5 males and 5 females selected at random were used for health check purposes. These animals were killed within 24 hours of arrival at HRC and subjected to routine macroscopic examination. Lungs, liver, kidneys, spleen and heart were preserved in fixative, but not processed further.

The remaining rats were placed at random in suspended cages with wire mesh floors, according to sex, so that each cage contained 5 rats of the same sex. Animal room temperature and relative humidity controls were set at 21 ± 2°C and 50 ± 10% respectively and lighting was controlled to give 12 hours light (8.00 a.m. to 8.00 p.m.) and 12 hours dark per 24 hours.

All rats had free access to tap water and SDS Rat and Mouse No. 1 modified maintenance diet, except as noted under "Laboratory investigations". There was no information available to the Study Director to indicate that any non-nutrient substance likely to influence the effect of the test material was present in the diet, or the tap water, both of which were routinely subjected to chemical analysis as detailed in Addenda 1 and 2.

Results of all the analyses were lodged in HRC archives.

After an acclimatisation period of seven days, each animal was weighed and the required number of animals were selected by discarding those animals furthest from the mean bodyweight. The remaining animals were then randomly assigned to cages, stratified by bodyweight, in such a way that the initial cage means were approximately equal. The appropriate numbers of cages were then allocated to each treatment group.

Study design

The study design was as follows:

Group	Colour code	Treatment level (mg/kg/day)	Animal numbers Males	Females
1	White	Control (0)	1 - 5	26 - 30
2	Yellow	1	6 - 10	31 - 35
3	Blue	3	11 - 15	36 - 40
4	Green	10	16 - 20	41 - 45
5	Red	30	21 - 25	46 - 50
		Health check group	51 - 55	56 - 60

The rats were housed 5 to a cage, unless the number was reduced by mortality. Each cage was identified by a coloured label according to group and each label was uniquely numbered with cage and study number. The cage number was tattooed on the leg of each rat in the cage. Within each cage identification was by earmark. The cages constituting each group were dispersed in the battery so that possible environmental influences arising from their spatial distribution were equilibrated, as far as possible, for all treatments (see Figure 1).

Prior to final assignment to the study the animals were subjected to a veterinary examination to ensure the selected rats were in a good state of health. A further period of acclimatisation of seven days was allowed between allocation of animals to groups and commencement of treatment. The spare animals were retained during this acclimatisation period to replace any rat showing signs of ill health. On the day of commencement of treatment these spare rats were removed from the study without further investigation.

Throughout the study the animals were housed in the Department of Toxicology, Barriered Rodent Building No. 4, Room 9.

Administration of test material

The test material, M&B 46,030, was administered as a suspension in 0.5% aqueous methylcellulose. A series of suspensions was prepared, the concentrations being chosen to give a constant dosage volume of 5 ml/kg bodyweight. Control animals received the vehicle alone at the same dosage volume.

The dosing suspensions were prepared freshly each day. The animals were dosed at approximately the same time each day where possible, using a suitably graduated syringe and a rubber catheter (Ch 8 or 10) inserted into the stomach. The dosage volume administered to individual rats was adjusted according to the most recent recorded bodyweight.

Treatment in this manner continued once a day, seven days a week, for a total of 2 weeks.

Observations

Dated and signed records of all activities relating to the day by day running and maintenance of the study within the animal unit as well as to the group observations and examinations outlined in this report were recorded in the Study Day Book.

The following observations were made during the course of the study:

Clinical signs and mortality

Individual animals were observed at least once daily for any signs of behavioural changes, reaction to treatment or ill health. These examinations were performed on each weekday, at suitable intervals after dosing.

Dated and signed records of appearance, change and disappearance of clinical signs were maintained on clinical history sheets for individual animals.

Further checks were made early in each working day and again in the afternoon to look for dead or moribund animals. This allowed post mortem examination to be carried out during the working period of that day. At weekends a similar procedure was followed except that the final check was carried out at approximately mid-day.

All rats found dead in the cage were subjected to detailed macroscopic examination and, where practicable, a full spectrum of tissue samples was preserved routinely in buffered 10% formalin (see "Terminal Studies").

Bodyweight

The weight of each rat was recorded at the time of allocation of animals to groups, on the day of commencement of treatment and twice weekly thereafter.

Food consumption

The quantity of food consumed by each cage of rats was recorded on a weekly basis. Food intake per rat (g/rat/week) was calculated using the amount of food given to and left by each cage in each group and the number of rats surviving in each cage.

Efficiency of food utilisation

Food conversion ratios were calculated, where appropriate, from bodyweight and food consumption data as weight of food consumed per unit gain in bodyweight.

Water consumption

Daily monitoring by visual appraisal of the water bottles was maintained throughout the study.

Water consumption was measured accurately, by weight, over daily periods during Week 2 for all cages in all groups.

(Note: Water was removed overnight from animals sampled for urinalysis)

Ophthalmoscopy

Before treatment commenced, the eyes of all allocated animals were examined. During Week 2, the eyes of all animals in the control and high dosage level groups were examined.

Prior to examination, the pupils of all animals were dilated using a Tropicamide ophthalmic solution ("Mydriacyl", Alcon Laboratories).

Laboratory investigations

During Week 2, samples of blood were withdrawn, under light ether anaesthesia, from the orbital sinus of all rats from each group and overnight urine samples were also collected from all rats from each group.

The blood samples collected were divided into tubes as follows:

EDTA anticoagulant	-	for haematological investigations
Citrate anticoagulant	-	for coagulation tests
Heparin anticoagulant	-	for the remaining biochemical tests

Food was removed overnight from animals sampled for laboratory investigations. Water was also removed overnight from animals sampled for urinalysis.

The estimations performed on blood and urine samples have been listed overleaf, together with an abbreviated title (for use in Appendices and Tables), the methods and the units of measurement applicable at the time.

(a) Haematology	Units
The following estimations were performed with an Ortho ELT-1500, using standard Ortho methods:	
Packed cell volume (PCV)	%
Haemoglobin (Hb)	g/dl
Red cell count (RBC)	$x10^6/mm^3$
Absolute indices were calculated as follows:	
Mean corpuscular haemoglobin concentration (MCHC) Hb (g/dl) x 100 ÷ PCV (%)	%
Mean corpuscular volume (MCV) PCV (%) x 10 ÷ RBC ($x10^6/mm^3$)	fl
Total white cell count (WBC Total)	$x10^3/mm^3$
Platelet count (Plts)	$x10^3/mm^3$
The following were performed using the appropriate methodology, as described below:	
Reticulocyte count (Retic) - Method of Dacie, J.V., and Lewis, S.M. (Practical Haematology, 1966, 3rd edit., 28)	% (of red cells)
Differential WBC counts - standard microscopy of blood smear, stained with modified Wright's stain, counting 100 cells.	
Neutrophils (N) Lymphocytes (L) Eosinophils (E) Basophils (B) Monocytes (M)	$x10^3/mm^3$
Cell morphology: If abnormal cells were observed when examining any stained slide, their presence or absence on each such slide examined was recorded and tabulated separately.	
Thrombotest (TT) - Owren, P.A. (Lancet, 1959, ii, 754)	s

(b) Biochemistry	
The following parameters were analysed with an Hitachi 737 Clinical Chemistry Analyser:	
Total Protein	g/dl
Albumin (Alb)	g/dl
Globulin (Glob) - By subtraction Total Protein (g/dl) minus Albumin (g/dl)	g/dl
Urea nitrogen (Urea Nitr)	mg/dl
Creatinine	mg/dl
Sodium (Na)	mEq/l
Potassium (K)	mEq/l

	Units
Calcium (Ca)	mEq/l
Inorganic phosphorus (P)	mEq/l
Chloride (Cl)	mEq/l
Cholesterol (Chol) - (Enzymatic assay)	mg/dl
Alkaline phosphatase (AP) Reaction temperature 30°C	mU/ml

The following parameters were analysed using a Roche Cobas Centrifugal analyser, using the appropriate BCL test kit:

Glucose (Hexokinase mediated assay)	mg/dl
Glutamic-pyruvic transaminase (GPT), also known as 'alanine aminotransferase' Reaction temperature 30°C	mU/ml
Glutamic-oxaloacetic transaminase (GOT), also known as 'aspartate aminotransferase' Reaction temperature 30°C	mU/ml

(c) Urinalysis

Volume	**ml**

pH - by pH meter

Specific Gravity (SG) - by refractometry, compared to water with a value of 1000

Protein - by Roche Cobas Centrifugal Analyser using modified method of Macart, M. and Gerbaut, L., (Clin. Chim. Acta., 1984, 141, 77) mg/dl

Qualitative tests

Total reducing substances.....Clinitest

Glucose
Ketones
Bile pigments
Urobilinogen
Haem pigments* .....Multistix

Clinitest and Multistix are diagnostic reagents obtained from Ames Company, Stoke Poges, England and are used as qualitative indicators of analyte concentration. Results are reported according to the following convention:

0 = negative
TR = 'trace' of analyte
\+ = 'small amount' of analyte
++ = 'moderate amount' of analyte
+++ = 'large amount' of analyte
* Reported as a positive or negative finding only

Microscopy

For microscopic examination, an aliquot of the urine sample was centrifuged at approximately 1500 'g' for 10 minutes and the resulting deposit spread on a microscope slide. The deposit was examined for the presence of the following:

Epithelial cells	(E)
Polymorphonuclear leucocytes	(P)
Mononuclear leucocytes	(M)
Erythrocytes	(R)
Organisms	(O)
Renal tubule casts	(C)
Sperm	(SP)
Other abnormal constituents	(A)

The grading of cell frequency in the centrifuged deposit was as follows:

0 = none found in any field examined
1 = few in some fields examined
2 = few in all fields examined
3 = many in all fields examined

Terminal studies

Post mortem examination

On completion of 2 weeks of treatment, all surviving rats were killed by carbon dioxide asphyxiation and subjected to the necropsy procedure indicated below. As the terminal procedures took 2 days to complete, the dosing of individually treated animals continued until the day prior to being killed. The duration of the treatment period, however, is quoted as being 2 weeks.

All superficial tissues were examined visually and by palpatation and the cranial roof removed to allow observation of the brain, pituitary gland and cranial nerves. After ventral midline incision and skin reflection all subcutaneous tissues were examined. The condition of the thoracic viscera was noted with due attention to the thymus, lymph nodes and heart.

The abdominal viscera were examined before and after removal. The urinary bladder was examined externally and by palpation. The gastro-intestinal tract was examined as a whole and the stomach and caecum were incised and examined. The lungs were removed and all pleural surfaces examined under suitable illumination. The liver was sectioned at intervals of a few millimeters. The kidneys were incised and examined. Any abnormalities in the appearance and size of the gonads, adrenals, uterus, intra-abdominal lymph nodes and accessory reproductive organs were recorded.

The following organs from all animals killed at the scheduled sacrifice were dissected free of fat and weighed:

adrenals	liver	testes
brain	ovaries	thyroid
heart	pituitary	uterus
kidneys	spleen	

The weights of major organs of individual rats dying or killed during the study were recorded at the discretion of the pathologist.

Preservation of tissues

Samples of all the tissues listed below from all animals were preserved in buffered 10% formalin (except eyes, which were preserved in Davidson's fixative).

adrenals*

alimentary tract* (oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, and rectum)

aorta

brain* (medullary, cerebellar and cortical sections)

eyes*

femur (with joint)

Harderian gland

head (to preserve nasal cavity, paranasal sinuses, oral cavity, nasopharynx, middle ear, teeth, lachrymal gland and Zymbal's gland)

heart*

kidneys*

larynx and pharynx

liver*

lungs* (all lobes and mainstem bronchi)

lymph nodes* (cervical and mesenteric)

mammary gland*

ovaries*

pancreas*

pituitary*

prostate*

salivary gland*

sciatic nerve

seminal vesicles

skeletal muscle

skin

spinal cord* (cervical level)

spleen*

sternum* (for bone and marrow)

testes* (with epididymides)

thymus* (where present)

thyroid* (with parathyroid)

tongue

trachea*

urinary bladder*

uterus* (corpus and cervix)

vagina

In addition, samples of any macroscopically abnormal tissues were routinely preserved, along with samples of adjacent tissue where appropriate.

This extensive list of tissues preserved was intended to satisfy any possible future requirements for further examination of tissues.

Histopathological examination

Tissues required for microscopic examination in this study are marked '*' in the above tissue list. These tissues were embedded in paraffin wax and sections cut at 4 micrometers were stained with haematoxylin and eosin.

Frozen sections of liver, fixed in buffered formalin, were cut on a cryostat at 12 micrometers and stained for fat with Oil Red O (ORO).

In the first instance histopathological examination was restricted to:

(i) Abnormal tissues from animals that died during the study, in an attempt to ascertain cause of death.

(ii) The specified list of tissues from all animals from the control group and all animals from the high dosage level group, killed at 2 weeks.

(iii) Any macroscopically abnormal tissue in any animal.

The investigations were extended to the lower dose groups for liver and thyroids as signs of treatment-related effects were noted at the high dose level.

Statistical analysis

All statistical analyses were carried out separately for males and females. Analyses were carried out using the individual animal as the basic experimental unit. Bodyweight data were analysed using weight gains.

The following sequence of statistical tests was used for bodyweight, organ weight and clinical pathology data:

(i) If the data consisted predominantly of one particular value (relative frequency of the mode exceeded 75%), the proportion of animals with values different from the mode was analysed by Fisher's test (1) and Mantel's test (2). Otherwise:

(ii) Bartlett's test (3) was applied to test for heterogeneity of variance between treatments. Where significant (at the 1% level) heterogeneity was found, a logarithmic transformation was tried to see if a more stable variance structure could be obtained.

(iii) If no significant heterogeneity was detected (or if a satisfactory transformation was found), a one-way analysis of variance was carried out. If significant heterogeneity of variance was present and could not be removed by a transformation, the Kruskal-Wallis analysis of ranks (4) was used.

(iv) Analyses of variance were followed by Student's 't' test and Williams' test (5) for a dose-related response, although only the one thought most appropriate for the response pattern observed was reported. The Kruskal-Wallis analyses were followed by the non-parametric equivalents of the 't' test and Williams' test (Shirley's test, (6)).

Where appropriate, analysis of covariance was used in place of analysis of variance in the above sequence. For organ weight data, the final bodyweight was used as a covariate in an attempt to allow for differences in bodyweight which might have influenced the organ weights.

References

1. Fisher, R.A., (1950), "Statistical Methods for Research Workers", Para. 21.02, Oliver and Boyd, Edinburgh.
2. Mantel, N., (1963), J. Amer. Statist. Ass., 58 : 690 - 700.
3. Bartlett, M.S., (1937), Proc. Roy. Soc. A, 160 : 268 - 282.
4. Kruskal, W.H. and Wallis, W.A., (1952/3), J. Amer. Satist. Ass., 47 : 583 - 621 and 48 : 907 - 912.
5. Williams, D.A., (1971/2), Biometrics, 27 : 103 - 117 and 28 : 519 - 531.
6. Shirley, E., (1977), Biometrics, 33 : 386 - 389.

Good laboratory practice

This study was conducted using the principles of Good Laboratory Practice as set forth in:

The United Kingdom Compliance Programme, Department of Health and Social Security, 1986.

Oraganisation for Economic Co-operation and Development, ISBN 92-64-12367-9, Paris 1982.

United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160, Federal Register, 29 November 1983.

Japan Ministry of Agriculture, Forestry and Fisheries, 59 NohSan, Notification No. 3850, Agricultural Production Bureau, 10 August 1984.

However, the study was not subjected to review by our Department of Quality Assurance.

Location of study records

All specimens, raw data and other documents generated at HRC during the course of this study, together with a copy of the final report, are lodged in the Huntingdon Research Centre Ltd., Archives, Huntingdon, England.

Procedures

The procedures used during the study were those documented in the relevant HRC Procedure Manuals.

PRE-TREATMENT HEALTH CHECK

Five males and five females, randomly selected as spares, were killed and subjected to macroscopic examination. No lesions indicative of the presence of infectious disease were noted. Following veterinary inspection, all animals allocated to the study were stated as being in good health.

MORTALITY (Appendix 7)

There was a total of 4 deaths during the study, as follows:

Rat 21♂ (30 mg/kg/day): Found dead on the morning of Day 5 of treatment

Rat 23♂ (30 mg/kg/day): Found dead on the morning of Day 4 of treatment

Rat 46♀ (30 mg/kg/day): Found dead on the morning of Day 5 of treatment.

Although there were no clinical or macroscopic findings to directly indicate the cause of death of these animals, these mortalities were considered to be due to treatment with M&B 46,030.

In addition, Rat 28♀ (Control) died following blood sampling on Day 14. This death was considered to be accidental.

Clinical and pathological findings for the decedents are included in Appendix 7.

CLINICAL SIGNS (Appendix 7)

The principal clinical sign shown by treated animals was muscular spasms, noted as follows:

Rat 47♀ (30 mg/kg/day): Muscular spasms noted on Day 2 of treatment, 2 hours after dosing and lasting 15 seconds

Rat 48♀ (30 mg/kg/day): Muscular spasms noted on Day 2 of treatment, 1 minute after dosing and lasting 4 minutes.

In addition, rigidity on handling lasting 20 seconds was noted for Rat 23♂ (30 mg/kg/day) on the day prior to being found dead.

Clinical signs for all animals are detailed in Appendix 7.

BODYWEIGHT (Figure 2, Table 1, Appendix 1)

Bodyweight losses were noted after 4 days of treatment for most surviving animals given 30 mg/kg/day and one female given 10 mg/kg/day. Group mean weight change, over this period for males given 10 mg/kg/day and for males and females given 30 mg/kg/day was significantly lower than that of respective controls.

However, this effect was transient; the weight gain of all male treated groups and females given 1, 3 and 10 mg/kg/day from Day 4 was comparable with respective controls, while that of females in the high dosage group was significantly greater than that of control.

FOOD CONSUMPTION (Table 2)

During the first week of treatment, the food consumption by males and females given 30, 10 or 3 mg/kg/day and females given 1 mg/kg/day was lower than that of respective controls to a dosage-related degree. This broadly correlated with the observed weight gains of treated groups described above. There were no notable group differences in food intake during the second week of treatment.

EFFICIENCY OF FOOD UTILISATION (Table 3)

Efficiency of food utilisation was estimated by calculation of food conversion ratios, presented in Table 3.

During Week 1, there was a pronounced inferior efficiency of food utilisation shown by males and females given 30 mg/kg/day, when compared with controls. This change reflected the marked effect on weight gain of these animals over the first 4 days of treatment.

The efficiency with which food was utilised by males and females in other treated groups during Week 1 and for all groups in Week 2 did not show pronounced variation from respective controls. Rather, the ratios reflected the observed differences in weight gain and food intake noted during the treatment period.

WATER CONSUMPTION (Table 4)

During Week 2 of treatment, the water consumption of males and females in treated groups showed some variation from respective controls. In particular, a lower intake was noted for all female treated groups in comparison with control. However, the results did not show any dosage-relationship and treatment with M&B 46,030 was not considered to have affected water consumption.

OPHTHALMOSCOPY (Appendix 2)

Ophthalmoscopic examination in Week 2 of the control animals and animals in the high dosage group did not reveal any effect of administration with M&B 46,030.

All ophthalmoscopic findings, detailed in Appendix 2, were consistent with the age and strain of rat used.

HAEMATOLOGY (Table 5, Appendix 3)

Investigation on Day 14 of treatment revealed a slight, but statistically significant higher mean packed cell volume, haemoglobin concentration and red cell count for males given 30 mg/kg/day. In the absence of any histopathological changes, no toxicological importance is attributed to these minor differences from control.

There were no other differences from control values in treated groups.

BIOCHEMISTRY (Table 6, Appendix 4)

The mean plasma globulin concentration for males given 3 or 10 mg/kg/day and for males and females given 30 mg/kg/day was significantly higher than that of respective controls. Associated higher total protein values were noted for these groups, although statistical significance was not attained.

Mean plasma cholesterol and urea nitrogen levels for males given 30 mg/kg/day were also significantly higher than those of control, although a similar finding was not evident in females.

Although possibly related to treatment, the above differences from control values noted on Day 14 of treatment are considered to be of doubtful toxicological importance. There were no other notable differences from control.

URINALYSIS (Table 7, Appendix 5)

Investigation on Day 12 of treatment revealed a few statistically significant differences from control values. However, none of these group differences were considered to represent an effect of treatment with M&B 46,030.

ORGAN WEIGHTS (Table 8, Appendix 6)

The following were considered to be related to treatment with M&B 46,030:

The mean liver weight of males and females given 10 or 30 mg/kg/day and females given 3 mg/kg/day was significantly greater than that of respective controls, following adjustment for final bodyweight.

The mean thyroid weight for all female treated groups was greater than that of control, attaining statistical significance at all dosage levels. However, there was no dosage-dependency. A similar trend was also noted for all male treated groups, also without dosage-dependency, but statistical significance was not attained.

There were no notable differences from control in other organs.

MACROSCOPIC PATHOLOGY (Table 9, Appendix 7)

There were no macroscopic findings considered to be attributable to treatment with M&B 46,030.

MICROSCOPIC PATHOLOGY (Table 10, Appendix 7)

The microscopic findings seen in the tissues examined are listed individually in Appendix 7. The incidence of all microscopic findings is summarised in Table 10.

The following comments are made in summary:

Liver:	Minimal centrilobular enlargement of hepatocytes was noted in 3/5 males given 10 mg/kg/day and 3/5 males given 30 mg/kg/day. A similar change was not noted in animals from the other treated groups, or in controls.
Thyroids:	Minimal or moderate follicular cell hypertrophy was noted in males and females given 3, 10 or 30 mg/kg/day in a dosage-related manner. One female given 1 mg/kg/day also showed minimal follicular hypertrophy with epithelial vacuolation, which was not seen in any other animal. The relationship of this finding to treatment remains equivocal.
	All other findings were considered to be associated with non-treatment related pathology and to be of no toxicological importance.

FIGURE 1

Group and cage arrangement in the battery

Group	Dosage level (mg/kg/day)	Cage numbers ♂	Cage numbers ♀	Animal numbers ♂	Animal numbers ♀
1	Control (0)	1	6	1 - 5	26 - 30
2	1	2	7	6 - 10	31 - 35
3	3	3	8	11 - 15	36 - 40
4	10	4	9	16 - 20	41 - 45
5	30	5	10	21 - 25	46 - 50

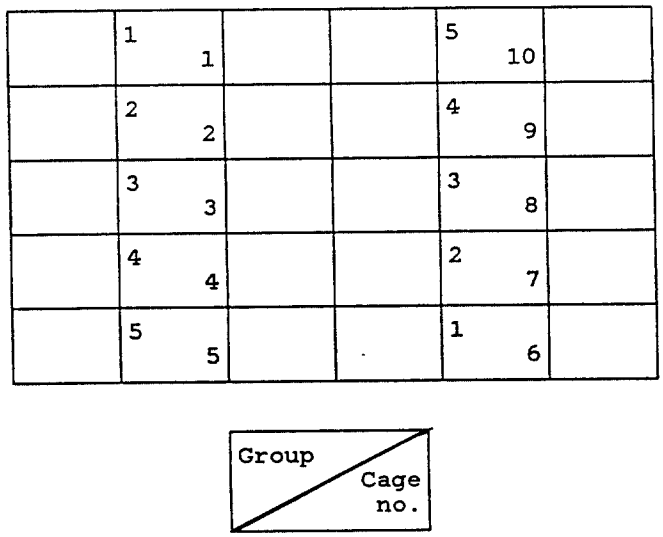

FIGURE 2

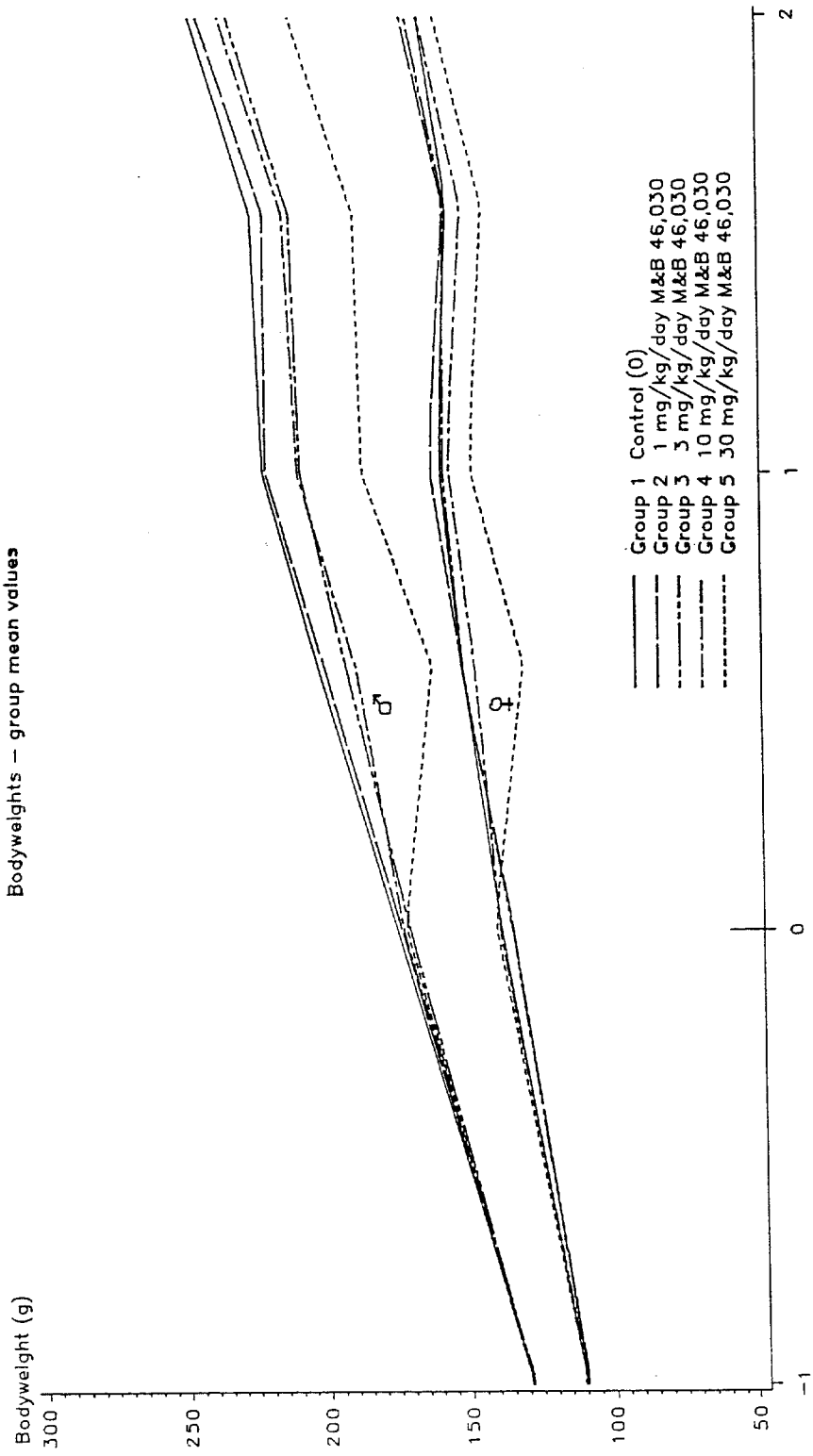
Bodyweights – group mean values
Bodyweight (g)
300
250
200
150
100
50
♂
♀
Group 1 Control (0)
Group 2 1 mg/kg/day M&B 46,030
Group 3 3 mg/kg/day M&B 46,030
Group 4 10 mg/kg/day M&B 46,030
Group 5 30 mg/kg/day M&B 46,030
−1
0
1
2
Week

TABLE 1

Bodyweights - group mean values (g)

Day	Group and dosage (mg/kg/day)									
	1♂ Control	2♂ 1	3♂ 3	4♂ 10	5♂ 30	1♀ Control	2♀ 1	3♀ 3	4♀ 10	5♀ 30
Pre-dose										
-7	128	129	129	128	129	110	109	110	110	110
Dosing										
0	175	173	170	173	171	138	134	134	139	140
4	202	200	192	188	161	151	151	151	146	129
7	221	220	208	209	186	158	161	157	155	147
11	225	220	211	213	188	154	155	155	149	142
14	246	243	232	236	210	165	171	169	164	159
Mean gain				**	**					**
Day 0 - 4	27	26	22	16	-9	13	17	16	8	-9
SD	3.1	5.1	2.2	4.5	8.5	3.6	5.1	3.6	7.9	11.9
Mean gain										**
Day 4 - 14	44	44	40	47	49	15	20	18	18	30
SD	8.8	10.8	5.7	6.7	4.2	5.1	6.0	6.0	3.2	10.2
Mean gain					**					
Day 0 - 14	71	70	62	63	40	27	37	34	26	21
SD	11.8	15.3	6.5	6.0	6.7	6.4	7.4	9.6	9.6	8.4

SD Standard deviation

Level of significance: Williams' test: ** P<0.01 in comparison with control

TABLE 2

Food consumption - group mean values (g/rat/week)

Week	Group and dosage (mg/kg/day)									
	1♂ Control	2♂ 1	3♂ 3	4♂ 10	5♂ 30	1♀ Control	2♀ 1	3♀ 3	4♀ 10	5♀ 30
Pre-dose -1	160	161	152	169	160	116	124	125	122	124
Dosing 1	176	175	158	158	98	137	126	121	110	83
2	145	143	138	144	130	111	107	108	103	106
Mean total Week 1 - 2	321	318	296	302	228	248	233	229	213	189
% of control	-	99	92	94	71	-	94	92	86	76

Statistical analysis not possible with only one cage per sex/group

TABLE 3

Food conversion ratios - group mean values

Week	Group and dosage (mg/kg/day)									
	1♂ Control	2♂ 1	3♂ 3	4♂ 10	5♂ 30	1♀ Control	2♀ 1	3♀ 3	4♀ 10	5♀ 30
1	3.8	3.7	4.2	4.4	6.2	6.9	4.6	5.3	6.8	8.7
2	5.9	6.2	5.6	5.4	5.3	14.4	11.6	9.1	10.8	9.0
1 - 2	4.5	4.6	4.8	4.8	5.5	9.2	6.4	6.6	8.3	8.8

Food Conversion Ratio = food consumption (g) / bwt gain (g)

TABLE 4

Water consumption - group mean values (g/rat/day)

Day	Group and dosage (mg/kg/day)									
	1♂ Control	2♂ 1	3♂ 3	4♂ 10	5♂ 30	1♀ Control	2♀ 1	3♀ 3	4♀ 10	5♀ 30
Dosing										
8	26.6	24.2	18.8	23.0	24.7	24.8	19.2	17.6	20.4	22.3
9	25.2	23.6	22.2	22.0	34.0	22.0	16.0	22.6	21.0	23.5
10	24.4	23.0	20.6	22.4	21.3	32.0	20.0	23.0	19.4	21.0
11	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
12	32.0	33.0	31.0	29.4	27.3	26.4	28.0	22.0	24.2	25.0
13	22.6	17.4	16.8	20.8	19.3	25.8	19.0	17.2	24.4	22.0
14	31.4	35.8	30.8	31.8	30.3	37.3	30.2	28.2	30.2	27.5
Mean total Week 2	162	157	140	149	157	168	132	131	140	141
% of control	-	97	86	92	97	-	79	78	83	84

NR Residue not recorded in error
Statistical analysis not possible with one cage per sex/group

TABLE 5

Haematology - group mean values

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	PCV %	Hb g/dl	RBC $x10^6$/ mm^3	MCHC %	MCV fl	WBC + Diff $x10^3/mm^3$						Plts $x10^3$/ mm^3	TT s
						Total	N	L	E	B	M		
1♂ Control	49	14.7	6.6	30.3	73	11.4	1.49	9.95	0.00	0.00	0.00 F	1358	22
2♂ 1	49	14.7	6.7	30.2	73	12.1	1.13	10.90	0.09	0.00	0.02	1061	25
3♂ 3	50	14.8	6.8	29.8	73	11.9	2.66	9.19	0.03	0.00	0.02	1255	25
4♂ 10	47	14.3	6.4	30.3	74	9.9	1.77	8.01	0.06	0.00	0.02	1285	25
5♂ 30	* 52	* 15.6	* 7.2	29.8	72	7.8	0.55	7.25	0.00	0.00	0.00	1165	31
1♀ Control	52	15.3	7.2	29.6	73	7.1	0.79	6.26	0.03	0.00	0.00	1103	20
2♀ 1	50	14.6	6.8	29.4	73	8.8	1.14	7.61	0.00	0.00	0.05	1040	21
3♀ 3	49	14.8	6.7	30.0	73	7.4	0.72	6.61	0.09	0.00	0.02	1081	21
4♀ 10	49	14.8	6.8	30.0	73	5.1	0.26	4.82	0.03	0.00	0.02	1291	22
5♀ 30	50	14.9	6.9	29.7	73	7.8	1.08	6.64	0.02	0.00	0.01	1126	(22)

F Analysis performed using Fisher's exact test followed by Mantel's test for trend in proportions

Level of significance: Williams' test: * $P<0.05$ in comparison with control

( ) Mean of 2 values

TABLE 6

Biochemistry - group mean values

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
		Total	Alb	Glob											
1♂ Control	111	6.2	3.2	3.0	9	F 0.4	435	30	62	143	3.8	5.5	5.1	97	75
2♂ 1	120	6.3	3.1	3.2	11	0.4	376	34	66	142	4.2	5.5	5.2	98	78
3♂ 3	110	6.6	3.1	* 3.4	11	0.4	414	37	68	143	3.7	5.5	5.1	97	85
4♂ 10	126	6.5	3.0	** 3.5	10	0.4	415	38	64	143	4.1	5.4	5.1	97	91
5♂ 30	125	6.7	3.1	** 3.6	** 14	0.4	409	37	55	143	3.5	5.6	5.1	95	** 120
1♀ Control	96	6.5	3.3	3.2	15	F 0.4	289	29	69	143	4.1	5.5	4.9	96	82
2♀ 1	105	6.5	3.2	3.3	15	0.4	257	27	70	142	3.7	5.4	4.6	97	93
3♀ 3	105	6.3	3.1	3.3	15	0.4	293	32	70	143	4.4	5.4	4.8	99	96
4♀ 10	105	6.6	3.1	3.5	15	0.4	249	31	60	142	3.9	5.6	4.6	97	110
5♀ 30	104	7.0	3.1	** 3.9	16	0.4	249	35	68	143	3.8	5.6	4.9	96	99

F Analysis performed using Fisher's exact test followed by Mantel's test for trend in proportions

Level of significance: Williams' test: * P<0.05
** P<0.01 in comparison with control

TABLE 7

Urinalysis - group mean values

Week 2 (10 October 1988)

Group/ dosage (mg/kg/day)	Vol- ume ml	pH	SG	Pro- tein mg/dl
1♂ Control	7.0	6.6	1027	93
2♂ 1	5.8	6.3	1028	77
3♂ 3	5.3	6.4	1031	94
4♂ 10	6.5	6.4	1030	91
5♂ 30	5.3	6.5	1029	* 66
1♀ Control	3.8	6.0	1038	40
2♀ 1	3.1	6.2	1042	42
3♀ 3	3.1	6.1	1038	41
4♀ 10	2.8	* 6.4	1038	48
5♀ 30	4.5	** 6.6	1031	38

Level of significance: Williams' test:
* P<0.05 in comparison with control
** P<0.01 in comparison with control

TABLE 8

Organ weights - group mean values

Group/ dosage (mg/kg/day)	Body wt. g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	Spleen g	Kidneys g	Adrenals mg	Testes g
1♂ Control	234	1.83 (1.81)	8.4 (8.0)	14.9	0.89 (0.85)	13.4 (12.5)	0.51 (0.48)	2.40 (2.30)	38.0	3.37
2♂ 1	232	1.81 (1.79)	8.2 (7.9)	17.1	1.06 (1.03)	14.5 (13.8)	0.54 (0.51)	2.13 (2.05)	44.8	3.33
3♂ 3	221	1.78 (1.79)	7.7 (7.8)	16.0	0.82 (0.83)	13.1 (13.4)	0.58 (0.59)	2.38 (2.42)	37.8	3.28
4♂ 10	226	1.81 (1.81)	10.4 (10.4)	18.6	0.87 (0.86)	14.5 * (14.4)	0.54 (0.53)	2.41 (2.40)	41.1	3.15
5♂ 30	202	1.86 (1.90)	7.6 (8.5)	17.7	0.72 (0.81)	14.7 ** (16.9)	0.43 (0.51)	1.91 (2.15)	40.8	3.03

Values shown in parentheses are adjusted for bodyweight
K Analaysis performed using Kruskal-Wallis test followed by distribution-free Williams'test
Level of significance: Williams' test: * P<0.05 in comparison with control
** P<0.01 in comparison with control

TABLE 8

(Organ weights - continued)

Group/ dosage (mg/kg/day)	Body wt. g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	Spleen g	Kidneys g	Adrenals mg	Uterus g	Ovaries mg
1♀ Control	162	1.71	9.4 (9.4)	10.6	0.71 (0.71)	7.5 (7.5)	0.41 (0.41)	1.60 (1.60)	49.7 K	0.52	60.0
2♀ 1	168	1.75	9.9 (9.4)	14.1 *	0.72 (0.70)	8.9 (8.5)	0.46 (0.44)	1.79 (1.69)	45.9	0.39	62.4
3♀ 3	163	1.73	9.4 (9.3)	13.9 *	0.65 (0.65)	8.9 (8.8) *	0.42 (0.42)	1.86 (1.84)	50.6	0.51	60.2
4♀ 10	158	1.72	10.7 (10.9)	13.3 *	0.65 (0.67)	9.3 (9.6) **	0.39 (0.40)	1.62 (1.68)	49.4	0.39	58.9
5♀ 30	157	1.73	11.3 (11.6)	16.9 **	0.64 (0.66)	10.1 (10.5) **	0.40 (0.41)	1.71 (1.79)	54.1	0.49	56.8

Values shown in parentheses are adjusted for bodyweight
K Analysis performed using Kruskal-Wallis test followed by distribution-free Williams' test
Level of significance: Williams' test: * P<0.05 in comparison with control
** P<0.01 in comparison with control

TABLE 9

Macroscopic pathology incidence summary

Group:	1	2	3	4	5
Test material:	Control	M&B 46,030			
Dosage (mg/kg/day):	0	1	3	10	30

	Males					Females				
	1	2	3	4	5	1	2	3	4	5
Rats on study:	5	5	5	5	5	5	5	5	5	5
Rats examined:	5	5	5	5	5	5	5	5	5	5
Thymus										
Left lobe, congested	0	0	0	0	0	1	0	0	0	0
Cervical nodes										
Enlarged	0	0	3	2	0	1	2	0	1	1
Liver										
Median cleft, a pale subcapsular area	0	1	0	1	1	0	0	0	0	1
Spleen										
Small	0	0	0	0	1	0	0	0	0	0
Uterus										
Fluid distension	0	0	0	0	0	2	1	2	1	1
Stomach, antrum mucosa										
Near to the limiting ridge, a white nodule	2	0	0	0	0	0	0	0	0	1
Skin										
Hairloss	1	0	0	0	0	0	0	0	0	2
Brain										
Congested	0	0	0	0	1	0	0	0	0	0
Oral cavity										
Lower incisors, pale	0	0	0	0	0	0	0	0	0	1

Sporadic, Terminal kill.

TABLE 10

Microscopic pathology incidence summary

Group:	1	2	3	4	5
Test material:	Control		M&B 46,030		
Dosage (mg/kg/day):	0	1	3	10	30

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
	MALES					FEMALES				
ANIMALS ON STUDY	5	5	5	5	5	5	5	5	5	5
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
TRACHEA										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
LUNGS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	0	0	0	0	1	0	0	0	0	0
LYMPHOID AGGREGATES (TOTAL)	5	0	0	0	2	4	0	0	0	4
MINIMAL	5	0	0	0	2	4	0	0	0	4
MEDIAL CALCIFICATION IN BLOOD VESSELS	1	0	0	0	0	0	0	0	0	0
HEART										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
THYMUS										
EXAMINED	5	0	0	0	3	5	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
CONGESTION	0	0	0	0	0	1	0	0	0	0
LYMPH NODES - CERVICAL										
EXAMINED	5	0	3	3	3	5	2	0	1	4
NO ABNORMALITIES DETECTED	5	0	1	0	3	4	0	0	0	4
LYMPHOID PROLIFERATION (TOTAL)	0	0	2	0	0	0	2	0	1	0
MINIMAL	0	0	2	0	0	0	2	0	1	0
REACTIVE HYPERPLASIA (TOTAL)	0	0	0	3	0	1	0	0	0	0
MINIMAL	0	0	0	3	0	1	0	0	0	0
LYMPH NODES - MESENTERIC										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
LIVER										
EXAMINED	5	5	5	5	5	5	5	5	5	5
NO ABNORMALITIES DETECTED	5	1	5	1	1	5	5	5	3	4

TABLE 10

(Microscopic pathology incidence summary - continued)

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
	MALES					FEMALES				
ANIMALS ON STUDY	5	5	5	5	5	5	5	5	5	5
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
LIVER (CONTINUED)										
CENTRILOBULAR HEPATOCYTE VACUOLATION -										
(TOTAL)	0	0	0	0	2	0	0	0	0	0
MINIMAL	0	0	0	0	2	0	0	0	0	0
GENERALISED HEPATOCYTE VACUOLATION -										
(TOTAL)	0	1	0	0	1	0	0	0	0	1
MINIMAL	0	1	0	0	0	0	0	0	0	0
CENTRILOBULAR HEPATOCYTE ENLARGEMENT -										
(TOTAL)	0	0	0	3	3	0	0	0	0	0
MINIMAL	0	0	0	3	3	0	0	0	0	0
CONGESTION	0	3	0	0	0	0	0	0	0	0
PARASITIC GRANULOMATA	0	0	0	1	0	0	0	0	0	0
GENERALISED HEPATOCYTE ENLARGEMENT -										
(TOTAL)	0	0	0	0	1	0	0	0	0	0
MINIMAL	0	0	0	0	1	0	0	0	0	0
INFLAMMATORY CELLS	0	0	0	0	1	0	0	0	1	0
MONONUCLEAR CELLS	0	0	0	0	0	0	0	0	1	0
LIVER (ORO STAIN)										
EXAMINED	5	0	0	0	3	3	0	0	0	4
NO ABNORMALITIES DETECTED	2	0	0	0	1	1	0	0	0	1
FAT DEPOSITION (TOTAL)	3	0	0	0	2	2	0	0	0	3
SLIGHT	3	0	0	0	2	2	0	0	0	3
SPLEEN										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
PANCREAS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
KIDNEYS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	3

TABLE 10

(Microscopic pathology incidence summary - continued)

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
	MALES					FEMALES				
ANIMALS ON STUDY	5	5	5	5	5	5	5	5	5	5
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
KIDNEYS (CONTINUED)										
HYDRONEPHROSIS (TOTAL)	0	0	0	0	0	0	0	0	0	1
MINIMAL	0	0	0	0	0	0	0	0	0	1
URINARY BLADDER										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
UTERUS										
EXAMINED	0	0	0	0	0	5	1	2	1	4
NO ABNORMALITIES DETECTED	0	0	0	0	0	2	0	0	0	2
DILATATION	0	0	0	0	0	3	1	2	1	2
CERVIX										
EXAMINED	0	0	0	0	0	4	0	0	0	4
NO ABNORMALITIES DETECTED	0	0	0	0	0	4	0	0	0	4
OVARIES										
EXAMINED	0	0	0	0	0	4	0	0	0	4
NO ABNORMALITIES DETECTED	0	0	0	0	0	4	0	0	0	3
FOLLICULAR CYSTS	0	0	0	0	0	0	0	0	0	1
PROSTATE										
EXAMINED	5	0	0	0	3	0	0	0	0	0
NO ABNORMALITIES DETECTED	5	0	0	0	3	0	0	0	0	0
TESTES										
EXAMINED	5	0	0	0	3	0	0	0	0	0
NO ABNORMALITIES DETECTED	5	0	0	0	3	0	0	0	0	0
THYROIDS										
EXAMINED	5	5	5	5	5	5	5	5	5	4
MISSING	0	0	0	0	0	0	0	0	0	1
NO ABNORMALITIES DETECTED	4	5	3	0	0	4	4	3	1	1

TABLE 10

(Microscopic pathology incidence summary - continued)

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
	MALES					FEMALES				
ANIMALS ON STUDY	5	5	5	5	5	5	5	5	5	5
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
THYROIDS	(CONTINUED)									
ECTOPIC THYMIC TISSUE	1	0	0	1	0	1	0	1	1	0
HYPERTROPHY OF FOLLICULAR EPITHELIUM - (TOTAL)	0	0	2	5	5	0	1	2	3	3
MINIMAL	0	0	2	4	2	0	1	2	2	3
MODERATE	0	0	0	1	3	0	0	0	1	0
EPITHELIAL VACUOLATION	0	0	0	0	0	0	1	0	0	0
PARATHYROIDS										
EXAMINED	5	4	5	5	5	5	5	5	4	4
MISSING	0	1	0	0	0	0	0	0	1	1
NO ABNORMALITIES DETECTED	5	4	5	5	5	5	5	5	4	4
ADRENALS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
PITUITARY										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
SALIVARY GLANDS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
OESOPHAGUS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
STOMACH										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	3	0	0	0	3	4	0	0	0	4

TABLE 10

(Microscopic pathology incidence summary - continued)

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
	MALES					FEMALES				
ANIMALS ON STUDY	5	5	5	5	5	5	5	5	5	5
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
STOMACH (CONTINUED)										
ECTOPIC NON-GLANDULAR EPITHELIUM - GLANDULAR REGION	2	0	0	0	0	0	0	0	0	0
DUODENUM										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
JEJUNUM										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
ILEUM										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	4	0	0	0	3	3	0	0	0	4
PROMINENT LYMPHOID FOLLICLES	1	0	0	0	0	1	0	0	0	0
CAECUM										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	2	4	0	0	0	4
PROMINENT LYMPHOID FOLLICLES	0	0	0	0	1	0	0	0	0	0
COLON										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
RECTUM										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
MAMMARY GLANDS										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
EYES										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4

TABLE 10

(Microscopic pathology incidence summary - continued)

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
	MALES					FEMALES				
ANIMALS ON STUDY	5	5	5	5	5	5	5	5	5	5
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
SPINAL CORD										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
BRAIN										
EXAMINED	5	0	0	0	4	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
CONGESTION	0	0	0	0	1	0	0	0	0	0
BONE MARROW/STERNUM										
EXAMINED	5	0	0	0	3	4	0	0	0	4
NO ABNORMALITIES DETECTED	5	0	0	0	3	4	0	0	0	4
*FACTORS CONTRIBUTORY TO DEATH										
EXAMINED	0	0	0	0	2	1	0	0	0	1
UNKNOWN	0	0	0	0	2	1	0	0	0	1

APPENDIX 1

Bodyweights - individual values (g)

Group 1♂ Control

Cage number	Animal number	Day					
		-7	0	4	7	11	14
1	1	128	187	219	243	254	276
	2	125	165	189	202	206	226
	3	132	172	199	219	222	248
	4	122	170	195	216	211	231
	5	134	180	207	227	231	249

Group 2♂ 1 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
2	6	126	171	202	221	224	246
	7	123	167	198	222	230	257
	8	132	182	210	233	232	257
	9	129	164	185	204	203	223
	10	134	182	203	221	212	233

Group 3♂ 3 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
3	11	132	172	192	206	210	228
	12	130	181	205	227	223	250
	13	125	164	187	200	202	220
	14	134	175	194	210	214	236
	15	123	159	182	196	206	228

(Bodyweights - continued)

Group 4♂ 10 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
4	16	123	154	170	184	192	208
	17	133	177	196	219	218	240
	18	128	181	198	217	222	245
	19	125	170	178	203	208	233
	20	131	181	200	221	227	252

Group 5♂ 30 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
5	21	127	176				
	22	126	170	170	189	198	218
	23	134	171				
	24	132	178	161	193	191	215
	25	124	162	152	175	175	198

(Bodyweights - continued)

Group 1♀ Control

Cage number	Animal number	Day					
		-7	0	4	7	11	14
6	26	107	136	152	160	157	172
	27	112	140	153	157	154	161
	28	112	140	156	162	156	
	29	105	141	149	162	156	166
	30	115	134	144	149	148	160

Group 2♀ 1 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
7	31	106	128	149	157	153	171
	32	113	130	151	159	151	162
	33	105	133	153	163	162	176
	34	110	134	147	164	160	173
	35	113	145	155	164	151	171

Group 3♀ 3 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
8	36	108	132	149	155	152	166
	37	105	131	143	148	140	153
	38	112	133	148	158	153	166
	39	113	135	151	156	158	169
	40	110	141	163	168	172	190

(Bodyweights - continued)

Group 4♀ 10 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
9	41	113	146	161	170	165	180
	42	107	132	147	158	152	168
	43	109	136	143	150	140	156
	44	105	124	120	128	125	137
	45	115	155	161	168	164	181

Group 5♀ 30 mg/kg/day

Cage number	Animal number	Day					
		-7	0	4	7	11	14
10	46	112	149				
	47	114	146	121	149	145	165
	48	111	138	129	145	140	149
	49	106	130	128	141	137	154
	50	108	136	138	153	145	167

APPENDIX 2

Ophthalmoscopy - individual observations

Group:	1	2	3	4	5
Test material:	Control		M&B 46,030		
Dosage (mg/kg/day):	0	1	3	10	30

Group	No. of rats examined	Rat no.	Eye	Observations
Pre-treatment (23 September 1988)				
1♂	5	-	-	-
2♂	5	9	R	Hyaloid remnants
3♂	5	15	B	Hyaloid remnants
4♂	5	17	B	Hyaloid remnants
		18	B	Hyaloid remnants
		20	B	Hyaloid remnants
5♂	5	-	-	-
1♀	5	-	-	-
2♀	5	-	-	-
3♀	5	40	L	Hyaloid remnants
4♀	5	43	R	Hyaloid remnants
5♀	5	-	-	-
Week 2 (11 October 1988)				
1♂	5	-	-	-
5♂	3	-	-	-
1♀	5	30	R	Intravitreal haemorrhage
5♀	4	-	-	-

R Right
L Left
B Both

Animals for which there were no ophthalmoscopic findings have been excluded from this Appendix.
Only control animals and animals in the high dosage group were examined in Week 2

APPENDIX 3

Haematology - individual values

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	PCV	Hb	RBC	MCHC	MCV	Retic	WBC + Diff x10³/mm³						Plts	TT
		%	g/dl	x10⁶/mm³	%	fl	%	Total	N	L	E	B	M	x10³/mm³	s
1♂ Control	1	46	14.3	6.1	31.1	75	<2.0	10.2	0.41	9.79	0.00	0.00	0.00	1319	21
	2	50	14.9	7.0	29.8	71	<2.0	12.0	0.60	11.40	0.00	0.00	0.00	1140	20
	3	47	14.3	6.2	30.4	76	<2.0	9.6	1.63	7.97	0.00	0.00	0.00	1421	23
	4	51	15.2	7.0	29.8	73	<2.0	14.2	1.99	12.21	0.00	0.00	0.00	1474	22
	5	49	14.9	6.8	30.4	72	<2.0	11.2	2.80	8.40	0.00	0.00	0.00	1435	24
	Mean	49	14.7	6.6	30.3	73		11.4	1.49	9.95	0.00	0.00	0.00	1358	22
	SD	2.1	0.40	0.44	0.54	2.1		1.80	0.993	1.841	0.000	0.000	0.000	134.5	1.6
2♂ 1	6	50	15.1	6.8	30.2	74	<2.0	10.8	0.86	9.94	0.00	0.00	0.00	1059	22
	7	46	14.1	6.2	30.7	74	<2.0	11.8	0.71	10.97	0.12	0.00	0.00	1051	22
	8	49	14.6	6.9	29.8	71	<2.0	11.7	0.59	11.12	0.00	0.00	0.00	1007	22
	9	48	14.1	6.8	29.4	71	<2.0	16.2	2.27	13.61	0.32	0.00	0.00	1131	23
	10	51	15.7	6.9	30.8	74	<2.0	10.2	1.22	8.87	0.00	0.00	0.10	1058	36
	Mean	49	14.7	6.7	30.2	73		12.1	1.13	10.90	0.09	0.00	0.02	1061	25
	SD	1.9	0.69	0.29	0.59	1.6		2.36	0.680	1.764	0.140	0.000	0.045	44.5	6.2
3♂ 3	11	49	14.6	6.6	29.8	74	<2.0	7.8	1.25	6.47	0.00	0.00	0.08	1107	24
	12	51	15.4	6.8	30.2	75	<2.0	11.5	1.61	9.89	0.00	0.00	0.00	1111	23
	13	48	14.5	6.6	30.2	73	<2.0	15.8	5.53	10.27	0.00	0.00	0.00	1255	35
	14	52	14.9	7.3	28.7	71	<2.0	17.2	4.13	12.90	0.17	0.00	0.00	1295	23
	15	48	14.5	6.6	30.2	73	<2.0	7.2	0.79	6.41	0.00	0.00	0.00	1506	22
	Mean	50	14.8	6.8	29.8	73		11.9	2.66	9.19	0.03	0.00	0.02	1255	25
	SD	1.8	0.38	0.30	0.65	1.5		4.54	2.061	2,763	0.076	0.000	0.036	163.7	5.4

SD Standard deviation
No changes in cell morphology noted

APPENDIX 3

(Haematology - continued)

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	PCV %	Hb g/dl	RBC $x10^6$/ mm^3	MCHC %	MCV fl	Retic %	WBC + Diff $x10^3/mm^3$ Total	N	L	E	B	M	Plts $x10^3$/ mm^3	TT s
4♂	16	49	14.5	6.6	29.6	74	<2.0	9.9	1.19	8.51	0.10	0.00	0.10	1331	23
10	17	48	14.6	6.6	30.4	73	<2.0	10.9	3.05	7.85	0.00	0.00	0.00	996	22
	18	46	14.2	6.1	30.9	75	<2.0	11.6	2.55	8.93	0.12	0.00	0.00	1143	32
	19	47	14.3	6.2	30.4	76	<2.0	7.2	1.08	6.05	0.07	0.00	0.00	1442	24
	20	46	14.0	6.3	30.4	73	<2.0	9.7	0.97	8.73	0.00	0.00	0.00	1513	CTD
	Mean	47	14.3	6.4	30.3	74		9.9	1.77	8.01	0.06	0.00	0.02	1285	25
	SD	1.3	0.24	0.23	0.47	1.3		1.67	0.962	1.171	0.056	0.000	0.045	213.6	4.6
5♂	22	50	15.1	6.9	30.2	72	<2.0	7.7	0.77	6.93	0.00	0.00	0.00	1213	22
30	24	52	15.4	7.1	29.6	73	<2.0	10.5	0.53	9.98	0.00	0.00	0.00	1328	50
	25	55	16.2	7.7	29.5	71	<2.0	5.2	0.36	4.84	0.00	0.00	0.00	953	22
	Mean	52	15.6	7.2	29.8	72		7.8	0.55	7.25	0.00	0.00	0.00	1165	31
	SD	2.5	0.57	0.42	0.38	1.0		2.65	0.206	2.585	0.000	0.000	0.000	192.1	16.2

SD Standard deviation
CTD Sample clotted
No changes in cell morphology noted

APPENDIX 3

(Haematology - continued)

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	PCV	Hb	RBC	MCHC	MCV	Retic	WBC + Diff						Plts	TT
								Total	N	L	E	B	M		
		%	g/dl	x10⁶/mm³	%	fl	%	x10³/mm³						x10³/mm³	s
1♀ Control	26	48	14.2	6.7	29.6	72	<2.0	4.3	0.60	3.70	0.00	0.00	0.00	1010	19
	27	54	15.7	7.6	29.1	71	<2.0	5.8	0.29	5.51	0.00	0.00	0.00	1021	20
	29	54	16.2	7.3	30.0	74	<2.0	11.3	1.70	9.49	0.11	0.00	0.00	1042	20
	30	51	15.1	7.0	29.6	73	<2.0	6.9	0.55	6.35	0.00	0.00	0.00	1337	22
	Mean	52	15.3	7.2	29.6	73		7.1	0.79	6.26	0.03	0.00	0.00	1103	20
	SD	2.9	0.86	0.39	0.37	1.3		3.01	0.625	2.419	0.055	0.000	0.000	156.9	1.3
2♀ 1	31	49	14.6	6.7	29.8	73	<2.0	9.1	1.82	7.19	0.00	0.00	0.09	1034	20
	32	50	14.7	6.9	29.4	72	<2.0	6.8	0.61	6.19	0.00	0.00	0.00	903	CTD
	33	49	14.2	6.7	29.0	73	<2.0	6.8	0.54	6.19	0.00	0.00	0.07	1036	20
	34	48	14.3	6.4	29.8	75	<2.0	12.3	1.72	10.58	0.00	0.00	0.00	1369	21
	35	52	15.2	7.1	29.2	73	<2.0	9.0	0.99	7.92	0.00	0.00	0.09	858	21
	Mean	50	14.6	6.8	29.4	73		8.8	1.14	7.61	0.00	0.00	0.05	1040	21
	SD	1.5	0.39	0.26	0.36	1.1		2.26	0.605	1.811	0.000	0.000	0.046	200.1	0.6
3♀ 3	36	47	13.9	6.5	29.6	72	<2.0	6.9	0.69	6.00	0.21	0.00	0.00	890	22
	37	51	14.9	7.0	29.2	73	<2.0	8.1	0.49	7.53	0.08	0.00	0.00	1471	20
	38	52	15.6	7.2	30.0	72	<2.0	7.6	0.61	6.84	0.08	0.00	0.08	1023	22
	39	49	14.8	6.6	30.2	74	<2.0	5.6	0.56	5.04	0.00	0.00	0.00	985	21
	40	47	14.6	6.3	31.1	75	<2.0	9.0	1.26	7.65	0.09	0.00	0.00	1038	22
	Mean	49	14.8	6.7	30.0	73		7.4	0.72	6.61	0.09	0.00	0.02	1081	21
	SD	2.3	0.61	0.37	0.72	1.3		1.28	0.309	1.097	0.075	0.000	0.036	225.3	0.9

SD Standard deviation
CTD Sample clotted
No changes in cell morphology noted

APPENDIX 3

(Haematology - continued)

Week 2 (12 October 1988)

Group/ Dosage (mg/kg/day)	Rat no.	PCV	Hb	RBC	MCHC	MCV	Retic	WBC + Diff x10³/mm³						Plts	TT
		%	g/dl	x10⁶/ mm³	%	fl	%	Total	N	L	E	B	M	x10³/ mm³	s
4♀	41	49	14.7	6.8	30.0	72	<2.0	5.8	0.29	5.51	0.00	0.00	0.00	1400	23
10	42	49	15.0	6.6	30.6	74	<2.0	3.6	0.40	3.13	0.00	0.00	0.07	1347	23
	43	48	14.2	6.7	29.6	72	<2.0	6.3	0.25	5.92	0.13	0.00	0.00	1197	21
	44	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
	45	51	15.1	7.1	29.6	72	<2.0	4.8	0.10	4.70	0.00	0.00	0.00	1218	20
	Mean	49	14.8	6.8	30.0	73		5.1	0.26	4.82	0.03	0.00	0.02	1291	22
	SD	1.3	0.40	0.22	0.47	1.0		1.19	0.124	1.232	0.065	0.000	0.035	98.6	1.5
5♀	47	50	14.8	6.9	29.6	72	<2.0	7.2	0.79	6.34	0.07	0.00	0.00	1222	21
30	48	53	15.8	7.4	29.8	72	<2.0	5.1	0.66	4.39	0.00	0.00	0.05	853	CTD
	49	50	14.7	6.8	29.4	74	<2.0	7.3	1.17	6.13	0.00	0.00	0.00	975	CTD
	50	48	14.3	6.6	29.8	73	<2.0	11.4	1.71	9.69	0.00	0.00	0.00	1454	23
	Mean	50	14.9	6.9	29.7	73		7.8	1.08	6.64	0.02	0.00	0.01	1126	22
	SD	2.1	0.64	0.34	0.19	1.0		2.64	0.471	2.215	0.035	0.000	0.025	267.2	1.4

SD Standard deviation
CTD Sample clotted
No changes in cell morphology noted

APPENDIX 4

Biochemistry - individual values

Week 2 (12 October 1988)

Group/ Dosage (mg/kg/day)	Rat no.	Glucose mg/dl	Protein g/dl Total	Alb	Glob	Urea Nitr mg/dl	Creatinine mg/dl	AP mU/ml	GPT mU/ml	GOT mU/ml	Na mEq/l	K mEq/l	Ca mEq/l	P mEq/l	Cl mEq/l	Chol mg/dl
1♂ Control	1	120	6.0	3.1	2.9	8	0.4	439	26	58	144	3.6	5.4	5.8	96	84
	2	131	6.5	3.3	3.2	10	0.3	428	31	63	142	4.1	5.5	5.1	97	77
	3	95	6.1	3.1	3.0	7	0.4	551	36	68	142	3.5	5.5	4.6	96	62
	4	85	6.3	3.3	3.0	10	0.4	348	27	65	143	3.7	5.4	5.1	98	73
	5	123	6.2	3.1	3.1	9	0.4	409	29	57	142	4.2	5.5	5.1	99	77
	Mean	111	6.2	3.2	3.0	9	0.4	435	30	62	143	3.8	5.5	5.1	97	75
	SD	19.7	0.19	0.11	0.11	1.3	0.04	73.8	4.0	4.7	0.9	0.31	0.05	0.43	1.3	8.1
2♂ 1	6	94	6.0	2.9	3.1	11	0.4	367	28	55	142	4.0	5.6	5.1	98	58
	7	141	6.1	3.1	3.0	9	0.5	404	33	51	142	4.1	5.5	5.3	97	88
	8	113	5.9	2.9	3.0	15	0.4	412	42	80	141	5.2	5.6	5.9	97	67
	9	116	6.4	3.1	3.3	10	0.4	389	32	68	142	3.9	5.4	5.0	97	80
	10	136	6.9	3.3	3.6	10	0.4	310	37	78	143	3.9	5.3	4.9	99	98
	Mean	120	6.3	3.1	3.2	11	0.4	376	34	66	142	4.2	5.5	5.2	98	78
	SD	19.0	0.40	0.17	0.25	2.3	0.04	40.9	5.3	13.1	0.7	0.55	0.13	0.40	0.9	16.0
3♂ 3	11	93	6.2	2.9	3.3	9	0.4	288	29	52	143	3.5	5.2	5.3	99	67
	12	127	6.4	3.2	3.2	11	0.4	536	45	81	143	3.9	5.5	5.0	99	98
	13	80	7.0	3.1	3.9	13	0.5	564	38	69	144	3.9	5.6	5.4	97	83
	14	119	7.0	3.4	3.6	12	0.4	321	38	77	142	3.8	5.5	4.7	96	86
	15	131	6.3	3.1	3.2	8	0.4	363	34	62	143	3.6	5.5	5.1	96	91
	Mean	110	6.6	3.1	3.4	11	0.4	414	37	68	143	3.7	5.5	5.1	97	85
	SD	22.4	0.39	0.18	0.30	2.1	0.04	127.0	5.9	11.6	0.7	0.18	0.15	0.27	1.5	11.6

SD Standard deviation

APPENDIX 4

(Biochemistry - continued)

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Glu-cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat-inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
			Total	Alb	Glob											
4♂	16	90	6.1	2.7	3.4	11	0.4	544	46	72	142	4.1	5.3	5.1	97	73
10	17	105	6.9	3.1	3.8	10	0.5	565	38	67	144	4.2	5.5	5.2	97	69
	18	122	6.5	3.0	3.5	12	0.4	279	38	64	142	4.3	5.4	5.5	96	100
	19	144	6.4	2.9	3.5	7	0.4	332	41	59	143	3.8	5.2	4.5	98	97
	20	168	6.4	3.2	3.2	10	0.4	356	29	59	142	3.9	5.5	5.2	97	115
	Mean	126	6.5	3.0	3.5	10	0.4	415	38	64	143	4.1	5.4	5.1	97	91
	SD	31.0	0.29	0.19	0.22	1.9	0.04	130.4	6.2	5.5	0.9	0.21	0.13	0.37	0.7	19.4
5♂	22	135	7.0	3.2	3.8	14	0.4	414	43	57	143	3.3	5.6	5.0	92	146
30	24	117	6.3	2.9	3.4	13	0.4	358	35	53	143	3.5	5.6	5.5	97	108
	25	123	6.9	3.3	3.6	15	0.4	455	34	54	142	3.7	5.7	4.9	96	107
	Mean	125	6.7	3.1	3.6	14	0.4	409	37	55	143	3.5	5.6	5.1	95	120
	SD	9.2	0.38	0.21	0.20	1.0	0.00	48.7	4.9	2.1	0.6	0.20	0.06	0.32	2.6	22.2

SD Standard deviation

APPENDIX 4

(Biochemistry - continued)

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
			Total	Alb	Glob											
1♀ Control	26	93	6.1	3.1	3.0	15	0.4	289	28	66	143	3.8	5.5	5.1	99	95
	27	110	7.0	3.4	3.6	16	0.5	227	27	69	141	3.9	5.4	4.2	95	71
	28	77	6.0	3.0	3.0	13	0.4	250	26	66	145	5.4	5.4	5.6	96	75
	29	107	6.6	3.4	3.2	13	0.4	367	32	67	141	3.7	5.6	4.9	96	89
	30	91	6.7	3.4	3.3	16	0.4	313	32	76	144	3.8	5.6	4.9	95	78
	Mean	96	6.5	3.3	3.2	15	0.4	289	29	69	143	4.1	5.5	4.9	96	82
	SD	13.3	0.42	0.19	0.25	1.5	0.04	54.8	2.8	4.2	1.8	0.72	0.10	0.50	1.6	10.0
2♀ 1	31	97	6.5	3.0	3.5	16	0.4	207	28	65	142	3.6	5.3	4.8	95	69
	32	114	6.5	3.3	3.2	14	0.4	264	26	67	142	3.5	5.3	4.0	97	107
	33	98	6.7	3.3	3.4	17	0.4	211	30	91	143	3.6	5.5	4.4	97	133
	34	99	6.4	3.2	3.2	16	0.4	238	26	56	141	3.9	5.7	4.9	98	72
	35	116	6.3	3.2	3.1	10	0.4	366	27	71	143	3.7	5.3	4.7	99	86
	Mean	105	6.5	3.2	3.3	15	0.4	257	27	70	142	3.7	5.4	4.6	97	93
	SD	9.4	0.15	0.12	0.16	2.8	0.00	65.0	1.7	13.0	0.8	0.15	0.18	0.36	1.5	26.7
3♀ 3	36	106	6.2	3.1	3.1	16	0.4	273	27	55	143	4.6	5.4	4.9	101	80
	37	95	6.3	3.0	3.3	17	0.4	183	27	56	142	4.8	5.5	5.0	98	117
	38	101	6.5	3.0	3.5	11	0.4	334	37	78	144	4.1	5.3	4.7	98	100
	39	110	6.5	3.2	3.3	16	0.4	270	36	88	143	4.6	5.4	4.9	100	103
	40	115	6.2	3.0	3.2	13	0.4	406	32	73	143	3.8	5.3	4.5	96	79
	Mean	105	6.3	3.1	3.3	15	0.4	293	32	70	143	4.4	5.4	4.8	99	96
	SD	7.8	0.15	0.09	0.15	2.5	0.00	82.9	4.8	14.3	0.7	0.41	0.08	0.20	1.9	16.2

SD Standard deviation

APPENDIX 4

(Biochemistry - continued)

Week 2 (12 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Glu- cose mg/dl	Protein g/dl			Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl
			Total	Alb	Glob											
4♀	41	96	6.2	3.0	3.2	14	0.4	282	24	58	144	3.9	5.5	4.9	98	124
10	42	108	6.5	3.2	3.3	15	0.5	295	30	57	143	4.0	5.6	4.6	97	113
	43	98	6.3	2.9	3.4	15	0.4	192	29	57	142	4.6	5.4	4.8	98	96
	44	104	7.3	3.2	4.1	19	0.5	228	39	72	142	3.4	5.6	4.2	94	115
	45	118	6.7	3.2	3.5	12	0.4	249	32	57	141	3.7	5.7	4.4	96	104
	Mean	105	6.6	3.1	3.5	15	0.4	249	31	60	142	3.9	5.6	4.6	97	110
	SD	8.8	0.44	0.14	0.35	2.5	0.05	41.5	5.4	6.6	1.1	0.44	0.11	0.29	1.7	10.7
5♀	47	95	6.9	3.1	3.8	19	0.4	207	39	84	143	3.5	5.5	4.9	97	71
30	48	102	7.2	3.1	4.1	14	0.4	314	36	66	143	3.8	5.6	5.0	94	136
	49	102	6.4	2.9	3.5	14	0.4	255	34	62	142	4.0	5.5	5.1	96	96
	50	117	7.3	3.3	4.0	15	0.4	221	30	59	143	3.7	5.7	4.6	96	93
	Mean	104	7.0	3.1	3.9	16	0.4	249	35	68	143	3.8	5.6	4.9	96	99
	SD	9.3	0.40	0.16	0.26	2.4	0.00	47.6	3.8	11.2	0.5	0.21	0.10	0.22	1.3	27.1

SD Standard deviation

APPENDIX 5

Urinalysis - individual values

Week 2 (10 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Vol- ume ml	pH	SG	Pro- tein mg/dl	Total red subs	Glu- cose	Ket- ones	Bile pig- ments	Uro- bili- nogen	Haem pig- ments	Microscopy						
												E	P	M	R	O	C	A
1♂ Control	1	11.0	6.5	1026	127	0	0	TR	0	0	0	0	0	0	0	1	0	0
	2	6.4	6.6	1026	79	0	0	TR	0	0	0	0	0	0	0	1	0	0
	3	7.2	6.4	1029	89	0	0	TR	0	0	0	1	0	0	0	1	0	0
	4	5.6	6.6	1028	78	0	0	TR	0	0	0	0	0	0	0	1	0	0
	5	4.8	6.7	1025	94	0	0	TR	0	0	0	0	0	0	0	1	0	0
	Mean	7.0	6.6	1027	93													
	SD	2.41	0.11	1.6	20.0													
2♂ 1	6	2.0	6.1	1033	105	0	0	TR	0	0	0	0	0	0	0	1	0	0
	7	4.2	6.4	1028	68	0	0	TR	0	0	0	0	0	0	0	1	0	0
	8	8.4	6.3	1027	72	0	0	TR	0	0	0	0	1	0	0	1	0	0
	9	5.0	6.2	1027	74	0	0	TR	0	0	0	0	0	0	0	1	0	0
	10	9.6	6.5	1025	66	0	0	TR	0	0	0	0	0	0	0	1	0	0
	Mean	5.8	6.3	1028	77													
	SD	3.12	0.16	3.0	16.0													
3♂ 3	11	3.2	6.3	1036	102	0	0	TR	0	0	0	0	0	0	0	1	0	0
	12	10.0	6.4	1025	88	0	0	TR	0	0	0	1	0	0	0	1	0	0
	13	2.8	6.6	1032	87	0	0	TR	0	0	0	0	0	0	0	1	0	0
	14	3.8	6.3	1035	106	0	0	TR	0	0	0	0	1	0	0	1	0	0
	15	6.8	6.3	1027	86	0	0	TR	0	0	0	0	0	0	0	1	0	0
	Mean	5.3	6.4	1031	94													
	SD	3.05	0.13	4.8	9.4													

SD Standard deviation
TR Trace

APPENDIX 5

(Urinalysis - continued)

Week 2 (10 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Volume ml	pH	SG	Protein mg/dl	Total red subs	Glucose	Ketones	Bile pigments	Urobilinogen	Haem pigments	Microscopy						
												E	P	M	R	O	C	A
4♂ 10	16	3.0	6.2	1042	116	0	0	TR	0	0	0	0	0	0	0	1	0	0
	17	8.6	6.3	1027	80	0	0	TR	0	0	0	1	0	0	0	1	0	0
	18	8.8	6.5	1027	81	0	0	TR	0	0	0	0	0	0	0	1	0	0
	19	6.8	6.4	1030	67	0	0	TR	0	0	0	1	0	0	0	1	0	0
	20	5.4	6.7	1026	112	0	0	TR	0	0	0	0	1	0	0	1	0	0
	Mean	6.5	6.4	1030	91													
	SD	2.41	0.19	6.7	21.6													
5♂ 30	22	6.6	6.4	1029	74	0	0	TR	0	0	0	1	0	0	0	1	0	0
	24	4.4	6.5	1026	57	0	0	TR	0	0	0	0	0	0	0	1	0	1SP
	25	4.8	6.5	1033	68	0	0	TR	0	0	0	1	0	0	0	1	0	0
	Mean	5.3	6.5	1029	66													
	SD	1.17	0.06	3.5	8.6													

SD Standard deviation
TR Trace
SP Sperm

APPENDIX 5

(Urinalysis - continued)

Week 2 (10 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Volume ml	pH	SG	Protein mg/dl	Total red subs	Glucose	Ketones	Bile pigments	Urobilinogen	Haem pigments	Microscopy E	P	M	R	O	C	A
1♀ Control	26	5.2	6.1	1035	39	0	0	0	0	0	0	1	0	0	0	1	0	0
	27	2.2	5.9	1043	42	0	0	0	0	0	0	0	1	0	0	1	0	0
	28	5.2	6.0	1033	33	0	0	0	0	0	0	1	0	0	0	2	0	0
	29	2.8	6.1	1044	41	0	0	0	0	0	0	1	1	0	0	1	0	0
	30	3.4	6.1	1033	43	0	0	0	0	0	0	1	0	0	0	2	0	0
	Mean	3.8	6.0	1038	40													
	SD	1.38	0.09	5.5	4.0													
2♀ 1	31	2.8	6.6	1042	60	0	0	0	0	0	+	1	1	0	1	1	0	0
	32	2.0	5.9	1047	44	0	0	0	0	0	0	1	0	0	1	1	0	0
	33	5.4	6.3	1041	29	0	0	0	0	0	0	0	0	0	0	1	0	0
	34	2.0	6.5	1034	29	0	0	0	0	0	0	0	0	0	0	1	0	0
	35	3.2	5.9	1045	47	0	0	0	0	0	0	1	1	0	1	1	0	0
	Mean	3.1	6.2	1042	42													
	SD	1.40	0.33	5.0	13.1													
3♀ 3	36	3.0	6.2	1031	26	0	0	0	0	0	0	0	1	0	0	1	0	0
	37	3.0	6.2	1037	39	0	0	0	0	0	0	0	0	0	0	1	0	0
	38	2.4	6.0	1046	59	0	0	0	0	0	0	1	0	0	0	1	0	0
	39	3.8	6.2	1032	34	0	0	0	0	0	0	1	1	0	1	1	0	0
	40	3.2	6.1	1042	49	0	0	0	0	0	0	1	1	0	0	1	0	0
	Mean	3.1	6.1	1038	41													
	SD	0.50	0.09	6.4	12.9													

SD Standard deviation

APPENDIX 5

(Urinalysis - continued)

Week 2 (10 October 1988)

Group/ dosage (mg/kg/day)	Rat no.	Volume ml	pH	SG	Protein mg/dl	Total red subs	Glucose	Ketones	Bile pigments	Urobilinogen	Haem pigments	Microscopy E	P	M	R	O	C	A
4♀ 10	41	2.6	6.6	1038	45	0	0	0	0	0	0	1	0	0	0	1	0	0
	42	3.2	6.5	1039	51	0	0	0	0	0	0	0	1	0	0	1	0	0
	43	1.2	6.3	1049	73	0	0	0	0	0	0	0	0	0	0	1	0	0
	44	2.0	6.3	1030	31	0	0	0	0	0	0	0	0	0	0	1	0	0
	45	4.8	6.2	1036	40	0	0	0	0	0	0	1	0	0	0	1	0	0
	Mean	2.8	6.4	1038	48													
	SD	1.36	0.16	6.9	15.8													
5♀ 30	47	3.2	6.4	1034	48	0	0	0	0	0	0	0	0	0	0	1	0	0
	48	6.4	6.4	1027	37	0	0	0	0	0	0	1	1	0	0	1	0	0
	49	4.2	6.7	1030	31	0	0	0	0	0	0	0	0	0	0	1	0	0
	50	4.0	6.8	1031	36	0	0	0	0	0	0	0	0	0	0	1	0	0
	Mean	4.5	6.6	1031	38													
	SD	1.37	0.21	2.9	7.2													

SD Standard deviation

APPENDIX 6

Organ weights - individual values

Group/ dosage (mg/kg/day)	Rat no.	Body wt. g	Brain g	Pitu-itary mg	Thyroids mg	Heart g	Liver g	Spleen g	Kidneys g	Adrenals mg	Testes g
1♂ Control	1	266	1.89	9.8	17.1	1.06	15.2	0.58	2.85	40.9	3.28
	2	215	1.78	8.6	12.7	0.83	13.4	0.44	2.16	29.7	3.19
	3	233	1.79	7.8	15.5	0.85	11.9	0.57	2.38	40.3	3.55
	4	221	1.79	6.5	14.7	0.79	11.4	0.43	2.28	32.6	3.21
	5	237	1.86	9.4	14.3	0.91	15.2	0.51	2.31	46.4	3.65
	Mean	234	1.83	8.4	14.9	0.89	13.4	0.51	2.40	38.0	3.37
	SD	19.8	0.051	1.32	1.61	0.105	1.80	0.072	0.265	6.75	0.212
2♂ 1	6	233	1.79	7.7	18.5	1.11	13.7	0.46	2.26	57.7	3.35
	7	247	1.79	9.2	16.0	1.19	17.2	0.61	2.36	37.2	3.27
	8	245	1.85	8.9	12.0	0.99	15.6	0.62	2.23	50.1	3.63
	9	213	1.80	7.7	20.8	0.81	12.2	0.53	1.74	38.1	3.17
	10	224	1.81	7.5	18.2	1.21	13.8	0.47	2.05	40.9	3.24
	Mean	232	1.81	8.2	17.1	1.06	14.5	0.54	2.13	44.8	3.33
	SD	14.3	0.024	0.79	3.32	0.164	1.90	0.073	0.243	8.84	0.177
3♂ 3	11	218	1.75	7.3	14.7	0.89	12.2	0.55	2.50	33.4	3.39
	12	216	1.85	6.8	19.2	0.80	14.3	0.49	2.50	42.7	2.86
	13	212	1.75	6.7	15.6	0.81	11.7	0.59	2.00	40.9	3.54
	14	223	1.78	9.0	13.2	0.81	14.2	0.75	2.68	38.1	3.33
	15	237	1.78	8.5	17.4	0.79	13.0	0.51	2.22	33.9	3.29
	Mean	221	1.78	7.7	16.0	0.82	13.1	0.58	2.38	37.8	3.28
	SD	9.7	0.042	1.04	2.34	0.041	1.16	0.106	0.269	4.13	0.255

SD Standard deviation

APPENDIX 6

(Organ weights - continued)

Group/ dosage (mg/kg/day)	Rat no.	Body wt. g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	Spleen g	Kidneys g	Adrenals mg	Testes g
4♂	16	202	1.76	9.1	16.9	0.87	12.4	0.50	2.38	39.0	2.80
10	17	231	1.88	10.3	10.8	0.81	15.3	0.59	2.65	43.8	3.54
	18	234	1.74	10.0	21.0	0.86	15.2	0.56	2.40	48.0	3.15
	19	219	1.84	12.4	16.9	0.81	12.8	0.46	2.11	36.9	3.17
	20	242	1.83	10.2	27.5	0.98	16.9	0.57	2.50	37.9	3.08
	Mean	226	1.81	10.4	18.6	0.87	14.5	0.54	2.41	41.1	3.15
	SD	15.6	0.058	1.21	6.16	0.067	1.90	0.056	0.196	4.67	0.263
5♂	22	212	1.98	8.3	18.4	0.83	17.9	0.55	2.09	50.3	3.10
30	24	205	1.81	7.8	19.4	0.68	14.1	0.47	1.91	37.2	3.17
	25	189	1.81	6.6	15.3	0.65	12.1	0.29	1.72	34.8	2.84
	Mean	202	1.86	7.6	17.7	0.72	14.7	0.43	1.91	40.8	3.03
	SD	11.8	0.097	0.87	2.14	0.098	2.96	0.131	0.185	8.34	0.175

SD Standard deviation

APPENDIX 6

Organ weights - individual values

Group/ dosage (mg/kg/day)	Rat no.	Body wt. g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	Spleen g	Kidneys g	Adrenals mg	Uterus g	Ovaries mg
1♀ Control	26	166	1.72	9.5	10.9	0.75	7.3	0.42	1.64	47.3	0.36	59.8
	27	158	1.65	8.5	8.6	0.64	7.3	0.42	1.53	58.3	0.38	55.2
	29	163	1.80	9.5	12.6	0.81	7.6	0.42	1.83	55.1	0.66	57.1
	30	160	1.67	10.2	10.2	0.64	7.8	0.36	1.42	37.9	0.66	67.9
	Mean	162	1.71	9.4	10.6	0.71	7.5	0.41	1.60	49.7	0.52	60.0
	SD	3.5	0.068	0.70	1.66	0.086	0.23	0.029	0.175	9.09	0.169	5.59
2♀ 1	31	168	1.78	10.6	13.9	0.75	10.4	0.55	1.78	61.0	0.39	85.0
	32	162	1.78	9.3	16.9	0.71	8.3	0.41	1.67	40.7	0.34	66.6
	33	173	1.76	11.0	12.1	0.75	8.7	0.46	1.77	39.4	0.28	54.6
	34	168	1.70	8.0	12.6	0.71	9.1	0.49	1.94	43.0	0.56	48.4
	35	169	1.73	10.4	15.0	0.68	8.2	0.38	1.77	45.5	0.38	57.6
	Mean	168	1.75	9.9	14.1	0.72	8.9	0.46	1.79	45.9	0.39	62.4
	SD	3.9	0.034	1.22	1.93	0.027	0.91	0.065	0.094	8.74	0.102	14.22
3♀ 3	36	161	1.80	9.7	11.7	0.61	9.0	0.45	1.90	47.1	0.36	68.0
	37	148	1.81	7.1	16.7	0.60	7.5	0.34	1.56	71.4	0.51	95.0
	38	161	1.67	11.2	13.9	0.64	8.2	0.35	1.95	41.7	0.62	45.4
	39	165	1.64	8.6	14.0	0.68	9.6	0.46	1.95	44.5	0.75	56.0
	40	181	1.74	10.5	13.0	0.74	10.0	0.49	1.94	48.5	0.31	36.4
	Mean	163	1.73	9.4	13.9	0.65	8.9	0.42	1.86	50.6	0.51	60.2
	SD	11.8	0.075	1.62	1.84	0.056	1.03	0.067	0.168	11.89	0.184	22.78

SD Standard deviation

APPENDIX 6

(Organ weights - continued)

Group/ dosage (mg/kg/day)	Rat no.	Body wt. g	Brain g	Pitu- itary mg	Thyroids mg	Heart g	Liver g	Spleen g	Kidneys g	Adrenals mg	Uterus g	Ovaries mg
4♀ 10	41	174	1.68	11.6	12.5	0.68	10.1	0.35	1.82	48.8	0.33	71.1
	42	161	1.75	9.3	15.4	0.63	8.7	0.41	1.46	50.5	0.31	55.2
	43	151	1.83	12.1	14.6	0.68	8.8	0.35	1.60	49.5	0.46	63.1
	44	131	1.55	10.2	11.8	0.58	7.9	0.34	1.13	48.2	0.46	42.1
	45	171	1.79	10.1	12.1	0.69	11.2	0.47	2.08	49.8	0.38	63.0
	Mean	158	1.72	10.7	13.3	0.65	9.3	0.39	1.62	49.4	0.39	58.9
	SD	17.4	0.112	1.15	1.61	0.046	1.31	0.057	0.360	0.89	0.069	10.95
5♀ 30	47	163	1.82	13.0	19.4	0.76	10.3	0.43	1.83	60.6	0.64	71.3
	48	149	1.74	9.9	13.9	0.59	8.9	0.35	1.69	50.1	0.55	48.7
	49	150	1.70	7.7	14.7	0.56	9.4	0.37	1.55	51.2	0.31	60.2
	50	165	1.65	14.4	19.4	0.66	11.9	0.43	1.79	54.3	0.45	46.9
	Mean	157	1.73	11.3	16.9	0.64	10.1	0.40	1.71	54.1	0.49	56.8
	SD	8.4	0.069	3.02	2.96	0.089	1.30	0.042	0.124	4.71	0.142	11.33

SD Standard deviation

Clinical and pathological findings for individual animals

Group:	1	2	3	4	5
Test Material:	Control		M&B 46,030		
Dosage (mg/kg/day):	0	1	3	10	30

In this appendix, the clinical, macroscopic and microscopic findings relating to each animal are listed on one page. These findings are presented by an automated data collation system and the following comments should be noted:

Particular care is taken during tissue removal and processing to ensure recovery and sectioning of all protocol-scheduled tissues. Understandably, omissions or irregularities can occasionally occur, the most vulnerable tissues in this regard being parathyroid, thymus, male mammary gland and autolysed portions of the gastro-intestinal tract. For each animal, any tissue so affected is listed as missing.

The following abbreviations are used:

WNL - Within normal limits

ORO - Oil Red O

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 1♂ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

Skin hairloss	Ventral surface.
Stomach, antrum mucosa	Near to the limiting ridge, a white nodule [1mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
STOMACH
Ectopic non-glandular epithelium - glandular region

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 2♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 3♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
ILEUM
Prominent lymphoid follicles

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 4♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

Stomach, antrum mucosa Near to the limiting ridge, a white nodule [1mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
Medial calcification in blood vessels
THYROIDS
Ectopic thymic tissue: (Unilateral)
STOMACH
Ectopic non-glandular epithelium - glandular region

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; LIVER (ORO stain) ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 5♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; LIVER (ORO stain) ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 6♂ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

Liver Median cleft, a pale subcapsular area [3mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Generalised hepatocyte vacuolation: (Minimal)

The following tissues were considered normal:
THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 7♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Congestion

The following tissues were considered normal:
THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 8♂ (Terminal kill)

CLINICAL FINDINGS

Right eye damaged during blood sampling on Day 14.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Congestion

The following tissues were considered normal:
THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 9♂ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 10♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Congestion

The following tissues were considered normal:
THYROIDS

Tissues not available for examination were:
PARATHYROIDS : (Not seen)

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 11♂ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes Enlarged.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Lymphoid proliferation: (Minimal)

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 12♂ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 13♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 14♂ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes Enlarged.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Lymphoid proliferation: (Minimal)
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 15♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes Enlarged.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LYMPH NODES - CERVICAL : (W.N.L.) ; LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 16♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 17♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes	Enlarged.
Liver	Median cleft, a pale subcapsular area [1mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Reactive hyperplasia: (Minimal)
LIVER
Parasitic granulomata: (some with haemorrhage)
THYROIDS
Hypertrophy of follicular epithelium: (Moderate)

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 18♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Reactive hyperplasia: (Minimal)
LIVER
Centrilobular hepatocyte enlargement: (Minimal)
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 19♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes Enlarged.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Reactive hyperplasia: (Minimal)
LIVER
Centrilobular hepatocyte enlargement: (Minimal)
THYROIDS
Ectopic thymic tissue
Hypertrophy of follicular epithelium: (Minimal ; Unilateral)

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 20♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Centrilobular hepatocyte enlargement: (Minimal)
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 21♂ (Sporadic)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

Found dead on Day 4.

MACROSCOPIC FINDINGS

Partially cannibalised.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)
*FACTORS CONTRIBUTORY TO DEATH
Unknown

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 22♂ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER
Centrilobular hepatocyte vacuolation: (Minimal)
Centrilobular hepatocyte enlargement: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
THYROIDS
Hypertrophy of follicular epithelium: (Moderate)
CAECUM
Prominent lymphoid follicles

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 23♂ (Sporadic)

CLINICAL FINDINGS

Pronounced salivation immediately before dosing on Day 4, followed by rigidity on handling lasting approximately 20 seconds. Appeared normal after dosing.

Found dead on Day 5.

MACROSCOPIC FINDINGS

	Partially cannibalised.
Brain	Congested.
Liver	Median cleft, a pale subcapsular area [1mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Generalised hepatocyte vacuolation: (Area)
Centrilobular hepatocyte enlargement: (Minimal)
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)
BRAIN
Congestion
*FACTORS CONTRIBUTORY TO DEATH
Unknown

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 24♂ (Terminal kill)

CLINICAL FINDINGS

No major signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Centrilobular hepatocyte enlargement: (Minimal)
THYROIDS
Hypertrophy of follicular epithelium: (Moderate)

The following tissues were considered normal:
TRACHEA ; LUNGS ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER (ORO stain) ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER PROSTATE ; TESTES ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 25♂ (Terminal kill)

CLINICAL FINDINGS

No major signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Spleen Small. (0.290g).

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER
Centrilobular hepatocyte vacuolation: (Minimal)
Generalised hepatocyte enlargement: (Minimal)
Inflammatory cells: (Foci) A few
LIVER (ORO stain)
Fat deposition: (Slight)
THYROIDS
Hypertrophy of follicular epithelium: (Moderate)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; SPLEEN : (W.N.L.) ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; PROSTATE ; TESTES PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 26♀ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of yellow fur staining was noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
ILEUM
Prominent lymphoid follicles

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; UTERUS ; CERVIX ; OVARIES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 27♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; LIVER (ORO stain) ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; UTERUS ; CERVIX ; OVARIES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 28♀ (Sporadic)

CLINICAL FINDINGS

Died following blood sampling on Day 14.

MACROSCOPIC FINDINGS

Cervical nodes	Enlarged [8mm].
Thymus	Left lobe, congested.
Uterus	Fluid distension [4mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
THYMUS
Congestion
LYMPH NODES - CERVICAL
Reactive hyperplasia: (Minimal)
UTERUS
Dilatation
THYROIDS
Ectopic thymic tissue: (Unilateral)
*FACTORS CONTRIBUTORY TO DEATH
Unknown

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 29♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
UTERUS
Dilatation

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; CERVIX ; OVARIES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: Control

Rat No/Sex: 30♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health or behavioural change noted during lifetime.

MACROSCOPIC FINDINGS

Uterus Bilateral uniform fluid distension [6mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
UTERUS
Dilatation

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; CERVIX ; OVARIES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 31♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes Enlarged.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Lymphoid proliferation: (Minimal)

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 32♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)
Epithelial vacuolation

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 33♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 34♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Cervical nodes	Enlarged.
Uterus	Fluid distension.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Lymphoid proliferation: (Minimal)
UTERUS
Dilatation

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

APPENDIX 7

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 1 mg/kg/day

Rat No/Sex: 35♀ (Terminal kill)

CLINICAL FINDINGS

No major signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 36♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
THYROIDS
Ectopic thymic tissue
Hypertrophy of follicular epithelium: (Minimal ; Unilateral)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

APPENDIX 7

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 37♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 38♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Uterus Fluid distension.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
UTERUS
Dilatation
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

APPENDIX 7

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 39♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

Uterus Fluid distension.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
UTERUS
Dilatation

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

APPENDIX 7

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 3 mg/kg/day

Rat No/Sex: 40♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS ; PARATHYROIDS

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 41♀ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Mononuclear cells: (Foci)
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 42♀ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of yellow fur staining was noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

APPENDIX 7

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 43♀ (Terminal kill)

CLINICAL FINDINGS

No major signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following tissues were considered normal:
LIVER ; THYROIDS

Tissues not available for examination were:
PARATHYROIDS : (Not seen)

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 44♀ (Terminal kill)

CLINICAL FINDINGS

Salivation noted after dosing on Day 14.

MACROSCOPIC FINDINGS

Cervical nodes	Enlarged.
Uterus	Fluid distension.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LYMPH NODES - CERVICAL
Lymphoid proliferation: (Minimal)
UTERUS
Dilatation
THYROIDS
Ectopic thymic tissue: (Unilateral)

The following tissues were considered normal:
LIVER ; PARATHYROIDS

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 10 mg/kg/day

Rat No/Sex: 45♀ (Terminal kill)

CLINICAL FINDINGS

No signs of ill health, behavioural change or reaction to treatment noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Inflammatory cells: (Foci)
THYROIDS
Hypertrophy of follicular epithelium: (Moderate)

The following tissues were considered normal:
PARATHYROIDS

Pathologist: S.K.Majeed

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 46♀ (Sporadic)

CLINICAL FINDINGS

Salivation and urogenital wetness noted after dosing on Day 4.

Found dead (partially cannibalised) on Day 5.

MACROSCOPIC FINDINGS

	Partially cannibalised.
Oral cavity	Lower incisors, pale.
Liver	Median cleft, a pale subcapsular area [1mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LIVER
Generalised hepatocyte vacuolation: (Area)
*FACTORS CONTRIBUTORY TO DEATH
Unknown

Tissues not available for examination were:
THYROIDS : (Not seen)
PARATHYROIDS : (Not seen)

Pathologist: S.K.Majeed

APPENDIX 7

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 47♀ (Terminal kill)

CLINICAL FINDINGS

Muscular spasms on handling 2 hours after dosing, lasting approximately 15 seconds on Day 2.

The incidental findings of brown nasal/fur staining and hair loss were noted during lifetime.

MACROSCOPIC FINDINGS

Uterus Fluid distension.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
KIDNEYS
Hydronephrosis: (Minimal)
UTERUS
Dilatation
OVARIES
Follicular cysts
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; LIVER (ORO stain) ; SPLEEN ; PANCREAS ; URINARY BLADDER ; CERVIX ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 48♀ (Terminal kill)

CLINICAL FINDINGS

Muscular spasms on handling 1 minute before dosing, lasting approximately 4 minutes on Day 2.

The incidental findings of red peri-orbital staining left eye and hair loss were noted during lifetime.

MACROSCOPIC FINDINGS

Skin hairloss General.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
UTERUS
Dilatation
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; CERVIX ; OVARIES ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 49♀ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

No abnormalities detected.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; UTERUS ; CERVIX ; OVARIES ; THYROIDS ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON ; RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

(Pathology - continued)

Compound: M&B 46,030

Dosage Level: 30 mg/kg/day

Rat No/Sex: 50♀ (Terminal kill)

CLINICAL FINDINGS

The incidental finding of hair loss was noted during lifetime.

MACROSCOPIC FINDINGS

Skin hairloss	Dorsum.
Cervical nodes	Enlarged.
Stomach, antrum mucosa	Near to the limiting ridge, a white nodule [1mm].

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:
LUNGS
Lymphoid aggregates: (Minimal)
LIVER (ORO stain)
Fat deposition: (Slight)
THYROIDS
Hypertrophy of follicular epithelium: (Minimal)

The following tissues were considered normal:
TRACHEA ; HEART ; THYMUS ; LYMPH NODES - CERVICAL : (W.N.L.) ; LYMPH NODES - MESENTERIC ; LIVER ; SPLEEN ; PANCREAS ; KIDNEYS ; URINARY BLADDER ; UTERUS ; CERVIX ; OVARIES ; PARATHYROIDS ; ADRENALS ; PITUITARY ; SALIVARY GLANDS ; OESOPHAGUS ; STOMACH : (W.N.L.) ; DUODENUM ; JEJUNUM ; ILEUM ; CAECUM ; COLON RECTUM ; MAMMARY GLANDS ; EYES ; SPINAL CORD ; BRAIN ; BONE MARROW/STERNUM

Pathologist: S.K.Majeed

Composition and quality assurance aspects of diet

SDS Rat and Mouse No. 1 modified maintenance diet is a closed formula diet. The standards of production adopted by the manufacturers have been approved by the HRC Quality Assurance Department.

Analyses were made of all batches of diet for most nutrients and for specified substances and micro-organisms likely to be present in feed ingredients or the finished diet and which, if in excess of specified amounts, might have had an undesirable effect on the test system. All batches of diet conformed with the acceptable standards agreed by the Study Director and HRC Department of Quality Assurance, as detailed below:

NUTRIENTS

		Target level	Tolerance (%)
Moisture	%	10.0	+25(max)
Crude fat	%	3.0	±30
Crude protein	%	14.5	±15
Crude fibre	%	4.0	±50
Ash	%	5.0	±25
Calcium	%	0.9	±30
Phosphorus	%	0.6	±20
Sodium	%	0.25	±40
Chlorine	%	0.5	±40
Magnesium	%	0.2	±50
Potassium	%	0.9	±50
Iron	mg/kg	200	±50
Copper	mg/kg	15	±60
Manganese	mg/kg	60	+60-40
Zinc	mg/kg	60	±50
Vitamin A	iu/kg	6000	-50
Vitamin E	mg/kg	70	-50

CONTAMINANTS	Maximum concentration (mg/kg)
Fluorine	20
Nitrates (as $NaNO_3$)	30
Nitrites (as $NaNO_2$)	10
Lead	2.0
Arsenic	1.0
Cadmium	0.7
Mercury	0.1
Selenium	0.6
Total aflatoxins	5.0 (µg/kg)
Total PCBs	0.05
Total DDT	0.25
Dieldrin	0.05
Lindane	0.30
Heptachlor	0.02
Malathion	5.0

MICROBIOLOGICAL CONTENT

	Maximum concentration (/g diet)
Total viable organisms	25000
Mesophilic spores	25000
Salmonella spp	0
Total coliforms	5
E. coli Type I	0
Fungal units	300

Quality assurance aspects of drinking water

Results of the routine physical and chemical examination of drinking water at source (Grafham Final Water) as conducted usually weekly by the supplier, Anglian Water Authority, were made available to HRC as quarterly summaries. Additionally, levels of specified substances known to be present from time to time in local water and which, if in excess of the maxima recommended (for humans) might have had undesirable effects on the test system, were determined in HRC tap water at approximately 6-monthly intervals.

Quarterly summary analyses of source water normally include levels of nitrites, nitrates, Ca, Mg, Na, K, P, Cl, Si, Fe.

Six-monthly analyses of HRC tap water currently include levels of As, Se, Ba, Ag, Sb, organophosphorus, organochlorine and other pesticides, haloforms, chlorophenols, polychlorinated biphenyls and polycyclic aromatic hydrocarbons.

Triage of 8(e) Submissions

Date sent to triage: MAY 0 5 1995 NON-CAP (CAP)

Submission number: 17645A TSCA Inventory: Y N (D)

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX (SBTOX) SEN WNEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: (0) 1 2 **pages** 42 **pages** 42, VTHS

Notes:

Contractor reviewer : PM **Date:** 4/26/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1192 - 12645 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Rhone - Poulenc Inc.

SUB. DATE: 10/27/92 OTS DATE: 11/03/92 CSRAD DATE: 03/01/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER RISKS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:
1H - Pyrazole - 3- carbonitrile, 5-amino - 1- [2,6 - dichloro - 4 - (trifluoromethyl)phenyl] - 4- [(trifluoromethyl) sulfinyl] -

CAS#
120068-37-3 → M+B 46030

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL. TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
(0213)	SUB ACUTE TOX (ANIMAL)	01 (02) 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
(0243)	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
(0248)	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:

NON-CBI INVENTORY: YES / NO / (IN ABEYANCE)

ONGOING REVIEW: YES (DROP/REFER) / NO (CONTINUE) / REFER

SPECIES: RAT

TOXICOLOGICAL CONCERN: LOW / MED / (HIGH)

USE: R&D pesticide

PRODUCTION: import

CAS SR

LOGGED: Beha - 0191 - 11625, 11795, 12325, 12845, 13155, 25405

-CPSS- 0927952113

0 0 0 0 0 0 0 0 0 0 0
> <ID NUMBER>
8(E)-12645A

> <TOX CONCERN>
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> <COMMENT>
SUBACUTE ORAL TOXICITY IN RATS IS HIGH CONCERN. GROUPS OF 10 (5/SEX) ANIMALS WERE EXPOSED TO 1, 3, 10, OR 30 MG/KG/DAY OF TEST MATERIAL FOR 7 DAYS FOR 2 WEEKS. MORTALITY OCCURRED AT THE 30 MG/KG/DAY DOSE LEVEL (2/5 M, 1/5 F). CLINICAL SIGNS INCLUDED MUSCULAR SPASMS, INITIAL WEIGHT LOSS, AND INITIAL DECREASE OF FOOD INTAKE. MEAN LIVER WEIGHTS WERE INCREASED IN MALES AT 10 AND 30 MG/KG/DAY AND IN FEMALES AT 3 MG/KG/DAY. MEAN THYROID WEIGHTS WERE INCREASED IN BOTH GENDERS AT ALL DOSE LEVELS. PATHOLOGICAL FINDINGS OCCURRED IN THE LIVER (MINIMAL CENTRILOBULAR HEPATOCYTE ENLARGEMENT) AND THYROIDS (MINIMAL OR MODERATE FOLLICULAR CELL HYPERTROPHY).

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